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Section of Psychiatry

President—W. D. Nicol, M.B., F.R.C.P.

[*November* 8, 1955]

DISCUSSION ON GERIATRIC PROBLEMS IN PSYCHIATRY

Dr. L. Z. Cosin: *The Organization of a Day Hospital for Psychiatric Patients in a Geriatric Unit*

So many old people will continue to live their lives and die at home in the family group that, as Sheldon has shown, incomparably the greater burden will not be borne by hospitals at all. In fact it is very desirable to attempt the further reduction, wherever possible, of accommodation for the elderly not in need of the fully organized and increasingly expensive hospital facilities.

The increased number of admissions of old folk to chronic sick hospitals and mental hospitals, while small as a percentage of the elderly population, is due in part to a failure to provide facilities in a field of preventive medicine, not yet completely explored.

Because the Oxford Geriatric Unit is exploring this field it is finding more and more examples of patients who can be discharged back to their own homes for greater or lesser periods of time, so that care by the family in selected cases can be supported by community and local authority efforts until it is desirable for medical or sociological reasons to readmit the old person to hospital on a permanent or temporary basis. This approach is especially valuable in the continued care of the elderly confused patients. The only previous solutions that have been offered have been admission to mental or chronic sick hospitals.

I had found previously, at Langthorne Hospital, in London, E.11, that early admissions of this type of patient for a temporary period of assessment, treatment of organic disease, and rehabilitation resulted in an increased willingness on the part of families to continue to care for their old people, as long as they were offered:

(1) A responsibility for a period of time that could be limited by the joint consultation and agreement of the family, the general practitioner and the Geriatric Unit's doctor and medical social worker.

(2) Intermittent periods of freedom from that responsibility by readmitting the patient for a short period to the hospital, so that summer holidays and rest periods could enable them to continue the responsibility for much longer than would otherwise be the case.

(3) In certain selected cases the Day Hospital regime has proved very helpful in affording methods of treatment of the patient, and relief of emotional stress in the family group, by removing the patient from the family during the daytime and returning him home to sleep in the evening. During the daily hospital stay the patient received physiotherapy in the form of the appropriate remedial exercises to enable him to get about with less pain and greater comfort, and incidentally to prevent accidents at home; more important still, the patient received occupational therapy which is a well-recognized form of treatment for the confused or psychiatric patient at any age. As a result, much nocturnal restlessness can be prevented and quiet nights obtained for the relatives and the patients. The occupational therapy should be given in a quiet room.

A very important part of this work consists of the co-ordination of the home and hospital environment which needs to be carried out by a medical social worker. I have found the services of the social worker in quietly overcoming home difficulties, keeping the hospital informed of progress at home, and assessing the build up of domestic emotional stresses, the latter to be reduced by appropriate temporary admission, of the greatest value; without this sociological assistance this method of treating many more patients without increasing the number of beds would have been infinitely more difficult.

The segregation of confused elderly patients in one part of the Geriatric Unit of the United Oxford Hospitals has provided the means of exploring some of the unsolved problems in this type of elderly patient. Many investigations have been made into the psychological and psychiatric variations of selected groups of patients in the higher age groups, but so far there seems to have been very little investigation into the possible solutions in the sociological and psychiatric fields of coping with the very rapidly increasing numbers of disturbed elderly people for whom there appears to be no other solution than lunacy certification.

The very coarse index of admission to mental hospitals, either voluntarily or under certification, is not adequate evidence of the incidence of major psychiatric disturbances in the elderly, but of the sociological collapse of a family or community situation. That situation has developed because the commonly occurring slow intellectual deterioration and decreasing ability to adjust rapidly in an elderly person has been complicated and worsened by several factors some of which are rapidly reversible. These include cerebral anoxia due to organic disease, cerebrovascular incidents and trauma. Of especial interest

is the incidence of intellectual deterioration following prolonged falls of systolic blood pressure due to major anæsthesia, post-operative surgical shock, and a combination of these two factors. Other factors are malnutrition involving protein, iron and vitamin-B deficiencies, emotional disturbances expressed as acute or long-standing anxiety states involving a family group, or individual dissonances in a household—to wit, the unsympathetic landlady of a furnished bed-sitting room. Other causes of financial, interpersonal or social stresses are often ascertained when an accurate history by a medical social worker is available. Thus, a mixed and complicated picture of slow and catastrophically rapid intellectual deterioration and emotional disturbances is only too often followed by certification and admission to a mental hospital.

For the last one hundred years various committees have drawn attention to the general undesirability of certifying very old people, and yet to-day more old people are being certified than ever before. This is due not only to their increasing numbers, but also to reduction in suitable hospital accommodation following 1929, 1939 and 1948.

These reductions in hospital beds are not necessarily disadvantageous, and can even become advantageous if we have the courage to reassess the problem and find new solutions to cope with this very old problem. An accurate reassessment of each confused individual's problems by means of the Geriatric Unit's team approach has given rise to a qualified optimism for this type of patient. As so many problems are indeed reversible and solvable it is necessary to solve them as rapidly as possible before the general practitioner is unwillingly faced with certification as his only solution.

By following this policy at Oxford in the last three years, a more optimistic end-result has become evident. After treating the reversible pathological causes of dementia we have concentrated upon reversible and remediable sociological causes, so that the underlying uncomplicated physiological intellectual deterioration or failure of adaptation can be recognized and handled in the most appropriate environment. This environment should be the family wherever possible, and we have been surprised to find how willing families are to continue to care for the confused parent or grandparent if the Geriatric Unit offers to help. This help includes:

(1) Immediate admission to break the vicious circle of family anxiety stress ⇄ increasing anxiety, depression and dementia in the old person.
(2) Follow up by the Geriatric Unit's social worker and doctor.
(3) Intermittent readmission for summer holidays and at other times during the year when stress on the family group begins to increase. The social worker is invaluable in watching this situation.
(4) Immediate readmission to the Geriatric Unit in the event of serious illness affecting the elderly patient or other member of the family group.
(5) The maintenance of optimal physical health utilizing physical medicine and occupational therapy.
(6) The sharing of responsibility for the patient during greater or lesser periods of each week. This is achieved by means of the Day Hospital which has been used in the Oxford Geriatric Unit for the last three years.

The Day Hospital is at present housed in the Occupational Therapy Department under the immediate control of the Superintendent Occupational Therapist. Patients usually enter the Day Hospital following discharge from the In-patient Department but this has been because the number of Day Hospital patients has had to be limited on account of shortage of space. There should be no difficulty in extending this service to suitable patients living in their own homes and before hospital admission becomes necessary, to anticipate a deteriorating family situation, so that it may well be prevented for many months. The decision to place a patient in the Day Hospital is arrived at in a staff conference attended by the clinician, the consultant psychiatrist, the social worker concerned with the case and the superintendent occupational therapist. The patients attend for from one to five full days a week and are given a midday meal in one of the ward day rooms. It is hoped to provide an independent dining room for these patients. Patients are brought to the Day Hospital by transport provided by the voluntary car service or the Local Authority.

Once in the Day Hospital the patients are given a programme of activities consistent with their ability. It is interesting to note what high standards of work are achieved by patients considered to be quite incapable of looking after themselves. Another activity in the O.T. Department consists of gradually increasing the old person's responsibility for himself, and then giving him minor duties caring for others.

Teams of patients co-operate in completing tasks no one patient could complete alone (this is not the genesis of a conveyor belt system or mass production lines). The occupational therapy is prescribed sometimes on an individual basis. Some patients suffering from chronic anxiety states or affective psychoses are given a small quiet corner where simple

uncomplicated work is provided, while the constant patience and reassurance of the occupational therapist helps to cope with any temperamental deterioration.

The social workers do much of their work by a quiet chat in the O.T. Department rather than by formal interview in an office. When, however, the latter is indicated it is immediately arranged. If medical advice or consultation is required a medical officer sees the patient, arranges immediate admission if necessary or communicates with the general practitioner. By this means the doubtful value of a hurried session with a doctor or social worker is replaced by a more leisurely and thorough interview of greater therapeutic value.

Regular communication between the family general practitioner, occupational therapist, medical social worker, clinician and psychiatrist provides for an increase or decrease in the number of days the patient attends each week.

There is provision for electro-convulsive treatment of patients with affective psychoses, in the Out-patient Department.

The standard of work by confused patients has been so high as to merit prizes in open competition with members of Women's Institutes.

Results.—During the first six months of 1953, of about 500 patients admitted to the Geriatric Unit of Cowley Road Hospital, 53 were suffering from confusion and dementia of major severity as diagnosed by the attendant Consultant Psychiatrist, Dr. J. E. Duffield. In addition, another group of 70 patients suffering from cardiac, respiratory or localized cerebral arteriosclerotic disease were considered to be certifiable at the time of admission. This latter group, however, lost their confusion as the disease from which they were suffering abated.

Thus about 25% of the 1,000 patients admitted a year are suffering from a sufficiently severe mental disturbance to warrant lunacy certification, while 11% or about 100 a year have long-term mental disturbances. An analysis of this latter group, which is roughly equivalent in numbers to the elderly patients admitted to the nearest mental hospital is as follows:

Discharged home	38%	
After improvement were resettled in private nursing homes or Long-stay Annexes	17%	
Total resettlement rate		55%
Died of intercurrent infection	17%	26%
Certified and transferred to mental hospitals	9%	
Were still resident four to ten months after admission	19%	
	100%	

Three-quarters of the discharged patients have attended the day hospital for from one to five days a week and are being helped to continue in their homes by this means. Apart from holiday readmissions for two to three weeks, few of the Day Hospital patients have needed emergency readmission although this will be inevitable.

It is hoped that by providing more accommodation it will be possible to increase the number of daily attendances to between 30 and 40 because there are four established needs not being met: (1) The numbers of discharged patients are being forced to reduce their number of daily visits per week. (2) Discharge of such patients is being held up, as it is not advisable without attendance at the Day Hospital. (3) Psychiatrists are requesting attendance at the Day Hospital for patients seen in consultation with General Practitioners. (4) A Preventive Mental Health programme to encourage the earlier treatment of needy patients cannot be considered in the existing overcrowded conditions.

With the increase of Day Hospital attendances from ten to thirty a day, an increased load of senile confused patients can be taken by the Geriatric Unit from the Mental Hospital, this preventing overcrowding and certification.

The mental health research team headed by Dr. F. Post, working in the Geriatric unit, has prepared a programme to evaluate among other factors the work of the Day Hospital.

The cost of providing care for such patients will be regularly compared with the cost of permanent institutional provision. Voluntary effort has been stimulated to co-operate in this community problem, and its value in the scheme may also become evident.

Conclusion.—A plan to extend an experiment of a day hospital for confused elderly patients in the Oxford Area is being completed. It will be a part of an existing Geriatric Unit and will reduce that moiety of patients now being certified and admitted to a mental hospital.

A research team working in the Geriatric Unit on the problems of senile confusion and dementia will examine the workings of the day hospital critically and publish the results. A financial examination of the national cost of each patient in this way will be compared with the national cost of permanent institutional accommodation.

This project in mental health and preventive care is suggested as a means of assisting the Health Service to adjust to the changing psychological and sociological problems of an ageing population.

Dr. Felix Post: *Some Research Problems in Old-Age Psychiatry*

Introduction.—In this account of research problems no attempt will be made to describe all current investigations into the mental aspects of ageing. I shall limit myself to problems with which I have been personally concerned. Most of the research was done from a 46-bedded unit for patients over 60 at the Bethlem Royal Hospital, which owes its establishment to Professor Aubrey Lewis; the investigations were carried out in close collaboration with members of the Institute of Psychiatry, especially Mr. M. B. Shapiro and young psychologists under his direction, and Dr. Vera Norris, lecturer in medical statistics.

Search for tests indicating the presence of early dementia.—In a unit receiving mainly aged patients with recent nervous and mental disorders we were especially interested to employ tests excluding the presence of early cerebral deterioration. However, after studying the literature on testing for intellectual impairment of elderly patients we came to the following conclusions: Gross and clinically obvious dementia is revealed in a low I.Q. on intelligence tests and in quotients indicative of deterioration such as the Babcock Efficiency Index; but where dementia is not severe or general, and therefore diagnostic tests most needed, impairment is not revealed by the I.Q. or by ratios comparing various subtests.

Goldstein and Scheerer (1941) suggested that while normal persons were capable of assuming both abstract and concrete attitudes in tackling tests such as the Weigl Colour-Form Sorting Test or the Kohs' Blocks Test, certain schizophrenics and all brain-damaged patients were limited to a concrete approach. As these tests appeared to be used in many centres for the diagnosis of early dementia, it was decided to try them out in some 50 patients of our geriatric unit. We also tested some 50 mentally well old people matched with the patients for sex, age and social background, and a group of healthy adults between the ages of 16 and 39. It was found that a large proportion of these young adults (18 of 46) were unable to assume, or to learn to adopt, the abstract attitude on both tests. However, in the majority of healthy subjects the abstract ability was preserved into the second half of the seventh decade; after the age of 68 the ability to assume the abstract attitude became increasingly rare. We were disappointed to find that only one psychiatric patient over 60 was able to adopt the abstract approach on all tests given. Most of the patients with a relatively small degree of concreteness were confirmed to be suffering from non-dementing syndromes, but complete inability to adopt the abstract attitude was not diagnostic of organic mental disorders. Most of the functional patients were suffering from affective illnesses, and our findings suggest that depression, at any rate in elderly people, is associated with difficulties in abstract thinking—that an affective disturbance in old people appears to be associated with a cognitive defect (Hopkins and Post, 1955).

The concept of an abstract mental attitude and the assumption that its loss occurs early in cerebral disorders are relatively recent theories. Impairment of memory in organic brain disease, in senile deterioration, and in old age has always been an accepted occurrence. Most traditional clinical tests for organic mental impairment purport to test memory, and they, along with several memory questionnaires, a New Word Learning Test, and four subtests of the Wechsler Bellevue Intelligence Test, were administered to 102 patients of the geriatric unit. Very briefly, most of the traditional tests, such as the name and address test, the rendering of various test stories, and the repetition of digits failed to differentiate between organic and functional patients; on the other hand, tests of orientation and some of the memory questionnaires concerning the patient's life, recent historical events, and the lay-out and routine of the hospital ward, did differentiate between groups of organic and functional mental patients at a significant level. Statistical analysis confirmed that these tests did, in fact, measure memory, and that memory was a function apart from general intelligence. But these memory tests were only successful in differentiating patients in terms of group distributions, and the overlap between the groups was so large that the tests are virtually useless in making a diagnosis of early dementia in individual elderly patients. To conclude: Though a general finding in established dementia, memory impairment is not, in many instances, one of the distinctive features of early cerebral deterioration in old people (Shapiro *et al.*, 1956).

Clinical studies of diagnosis and prognosis.—Our failure to validate tests of early dementia applicable to elderly patients may not be very important, since the difficulties of differentiating between the functional psychoses and the organic dementias of old age on purely clinical grounds have in the past been exaggerated. Between 1937 and 1943 the junior psychiatrists in the private wards of the Royal Edinburgh Hospital differentiated, on the whole successfully, 87 patients over 60 with affective illnesses from 125 arteriosclerotic and senile psychotics (Post, 1944). In one-third of all manic-depressives and involutional melancholics admitted for the first time between 1947 and 1949 to three London mental hospitals the diagnosis of affective disorder was made in spite of the fact that the patients were, at the time, over 60 years old (Norris, 1955). Using case records only, it was possible to distinguish between elderly patients suffering from organic or functional psychoses respec-

tively, and to demonstrate the correctness of this categorization by the striking differences in outcome of the two groups (Post, 1951).

To test the assumption that differential diagnosis as between the functional and the organic psychoses is fairly easy in the great majority of elderly mental patients, two investigations were carried out. In our out-patient clinic for patients over 60 some 190 consecutive referrals were diagnosed in many instances as suffering from recent affective illnesses and usually recommended for short-term hospital treatment; or a diagnosis of long-standing nervous or mental disorder, or of organic dementia was made; in these last two groups the recommendations were generally for long-term management or care. A twelve to eighteen months' follow-up showed that the recommendations had in a significantly large majority of cases been successful, presumably because the diagnoses on which they had been based had been correct (Norris and Post, 1954). In a second study, concerning 230 patients of a mental observation ward, we were able to confirm the relatively good early prognosis of clear-cut functional psychoses of old age. We picked out correctly, within ten days from admission, 85% of all patients who survived the first year after admission, and 71% of those who were discharged from psychiatric care during this period. We were disappointed in our hopes of being able to predict death or recovery at an early date after admission. But an analysis of our clinical data in the light of the follow-up results allowed us to work out a number of indicators which, especially when present in various combinations, were associated with early death or failure to recover. These were, of course, great age and the presence of serious physical disease, and we also confirmed the grave prognostic significance of acute organic confusional states; more surprising were the severely adverse effects of symptoms and signs of focal cerebral disease, and of severe degrees of social isolation, while living alone or the widowed state were not prognostically important. An interesting finding, deserving further study, was that the outlook in organic psychoses was significantly better in patients who showed some affective, paranoid, or neurotic symptoms in the organic setting, and who were not just suffering from a simple, featureless dementia (Kay *et al.*, 1956). The results of these two studies are in agreement with Roth (1955) who recently brought up to date and summarized his earlier findings suggesting strongly that in old age affective psychosis and late paraphrenia are largely independent of the senile and arteriosclerotic dementias.

Significance of affective symptoms in the aged.—It is, no doubt, intellectually satisfying to bring order into the ever-increasing multitude of mentally ill old people which fills our wards and out-patient departments, by dividing it into diagnostic and prognostic streams, and diagnostic classification has also proved useful in allowing us to make correct recommendations of treatment or management in a significantly large proportion of cases, using the term significant in the statistical sense. But in assessing and treating individual patients, young or old, we have always been aware of the shortcomings of diagnostic categories. To illustrate the limited usefulness of reaction types, we need not have recourse to the role of imponderables, such as personality factors, family constellations, or social factors of wider significance in shaping the course of an illness; we can draw on some concrete clinical facts. Roth (1955) discovered affective symptoms, though not always of melancholic depth or structure, at one stage of the illness in 6% of senile dements and 30% of arteriosclerotic psychotics. In a group of 189 patients with a manic or depressive symptom complex of at least a few weeks' duration Kay *et al.* (1955) found that only 14 patients were also suffering from organic mental symptoms; but after a brief period varying between only nine and twenty-seven months, 4 further patients had developed definite cerebral-organic signs. The organic features of most of these patients were due to arteriosclerotic brain disease, but these workers did not think that there was at present any clear evidence to support the assumption that the incidence of cerebral arteriosclerosis is higher in elderly manic depressives than in the general population of the same age. All the same, the impression persists that an unduly high proportion of old people originally admitted with an affective illness later on experience cerebrovascular or coronary accidents.

It seems likely that even long-term observation of old people with affective illnesses will show that the proportion of patients finally succumbing to arteriosclerotic or senile dementia will remain small. On the other hand, clinical experience shows that in spite of the relative ease and frequency with which elderly depressives can be discharged from hospital after relief of their symptoms with electro-convulsive therapy, many patients relapse almost immediately, and others have frequent recurrences with ultimate failure to respond to physical treatments. Almost certainly the readmission rate is higher than the 30% found by Norris (1955) for an average follow-up period of three and a half years of manic-depressive and involutional cases of all ages admitted to three London mental hospitals. Kay *et al.* (1955) found that only 38% of manic-depressives over 60 had remained well during a much shorter follow-up period. An impression has arisen that many patients, while not requiring mental hospital care, appear to subside into a state of mental invalidism

characterized by apathy or mild querulous depression, and by repetitive hypochondriacal complaints, intractable pains, odd tremors, and gait disturbances. All these resemble hysterical conversion symptoms of younger people, but are more likely to be due to little understood degenerative lesions of the central nervous system. These patients, though retaining their intellectual powers, cease to make use of them, and may become an even greater emotional and economic burden on their families than senile dements.

On the basis of a six-year follow-up of 100 consecutive depressive patients over 60 admitted under my care, we are at present attempting to define factors associated with different types of outcome. Also, we hope to confirm or to demolish a hypothesis according to which, expressed in over-simplified form, depressive illness in old age may take the form of either a phasic disorder or of a continuous process. Periodic depressions with return to the usual level of adjustment may continue into old age or, as is well known, may first originate during the senium. On the other hand, a depressive illness may either persist and assume an empty and stereotyped symptomatology, or affective disturbances may become easily and repeatedly precipitated in a setting of a depressive personality change characterized by a constantly gloomy, plaintive or querulous mood and hypochondriacal, quasi-obsessional, or mildly paranoid preoccupations. In a recent study of old people in the community Busse and his fellow-workers (1955) found that a significant proportion of subjects reported a definite increase in frequency and depth of depressive episodes with increasing age. In fact, nearly 50% of these old people living in their own homes reported apparently reactively produced mood disturbances varying in length from a few hours to several days, and occurring on the average once a month. A depressive personality change may thus be looked upon as a pathological exaggeration of the emotional changes brought about by normal ageing, much as senile dementia has been interpreted in terms of an acceleration of normal intellectual decline in old age. If the existence of a process of senile deterioration of affect apart from intelligence could be confirmed as a recognizable clinical picture, we should have to accept that in some patients it would not be sufficient to treat the individual attack of depression, but that we will have to cast about for means of preventing or, at any rate, of mitigating a state of increasing mental invalidism.

In the meantime, we have a much more urgent problem on our hands concerning the treatment of people suffering from the dementing illnesses of old age. Norris (1955) estimates that in London the expectation at birth of being admitted at least once to a psychiatric hospital for senile, presenile, or arteriosclerotic dementia is as high as for all other psychotic disorders taken together; but even in big cities a large proportion of mentally senile people never enter mental hospitals. I was, therefore, very glad to join Dr. Cosin and his group in an attempt to find better methods of treating persistently confused old people admitted to the Geriatric Unit of the United Oxford Hospitals. Having developed a system of ratings which will enable us to pick out matched samples of patients with senile or arteriosclerotic dementia, we are about to embark on a series of experiments with small groups of patients. It is well known that in most cases of old-age psychosis disturbed behaviour subsides very rapidly with the treatment of any physical disorder present and with skilled nursing care. But we are then left with persons who, while still receiving much attention from the environment, show little activity in an outward direction. Most actions are aimless or stereotyped, and are not used to achieve effective communication, in Ruesch and Bateson's (1951) sense. An attempt will be made to discover the kinds of action from the environment, coming from other patients, from nurses, from occupational therapists, and from the psychologist employing a variety of approaches, which can be shown to stimulate the patient into reciprocal purposive activity.

By rebuilding the demented patient's system of communications with the people and objects around him, we hope to retard the progress of further mental deterioration. Any measures showing promise in the experimental situation with hospital inmates might be employed with greater benefit in the out-patient department or day hospital with senile people still looked after by their families.

Summing-up.—On the whole, we have failed to develop tests of early dementia as seen in senescent patients. The only measure which, so far, has shown any real promise is the Bender Gestalt Test, which involves the copying of simple designs. This test is in the process of being refined and developed. But of greater importance is the fact that this is leading us into investigating more closely perceptual, motor, or other defects in some kinds of elderly psychotics. This is what has been happening to us again and again: we start work on a practical clinical problem and find that it either forces us to take up more basic problems of ageing, or that it links up with a general psychiatric question. Another small contribution to basic problems of ageing has been made in defining age changes in the ability of abstract thinking; further investigation of the discovery that old people with affective illness without brain damage decline from the abstract capacity level prematurely may throw light on the relationship between the cognitive and the orectic functions of

the personality. The occurrence of memory impairment apart from general intellectual decline has been confirmed, though in old people its presence, especially as indicated by many traditional clinical procedures, is not a reliable sign of rapidly progressive, and therefore practically significant, dementia. But here again we are led towards a more basic investigation of memory function as seen in various types of psychiatric illness in old age.

Prognostic studies have confirmed that, in terms of group statistics, the various psychiatric disorders of old age can be easily and successfully differentiated on clinical grounds alone. But we are still faced with a problem: Though old people with so-called functional, and especially with affective, mental syndromes, may live longer than arteriosclerotic or senile dements, and may be more frequently discharged from hospital care, yet the outcome in terms of the individual person's adjustment, well-being, and future mental health may vary considerably from case to case. A hypothesis according to which affective illness in old age may in some cases show periodic swings similar to those in younger people, but that in others it may present a process of affective deterioration, is being tested by a long-term study of a group of aged depressives. The interplay between personality structure, as it is seen to evolve in the course of a lifetime, and physical, psychological and interpersonal disturbances, is one of the many problems of general psychiatric interest which can be surveyed especially well from the vantage point of old age psychiatry.

Finally, I have indicated the general lines along which controlled experiments are designed to discover ways of improving the adjustment of old people with senile deterioration.

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Professor Martin Roth: It is useful, on occasion, to consider briefly some of the more basic causes of the problems that we are facing. They are biological and sociological.

Sociological factors, which have a more immediate bearing on our practical problems, arise from the transformation in the pattern of social life during the last century which has forced so many of the old into an existence isolated from the family in which formerly they held a positive, secure, and respected role. The authority wielded by the aged was not always a healthy influence within the family, a fact that is sometimes forgotten. But the change in their status has been swift and has brought many problems in its train. There are other psychological stresses, which, though more insidious, are no less devastating in their effects on the mental health of old people. These are the universal emphasis on the desirability of youth and youthful middle age which have become such prominent features of the culture of our time and of the business advertisement, magazine literature, and the mass organs of information and diversion which help to mould its ethos. The trend is perhaps most clearly manifest in the U.S.A., where the ghoulish artistry of the mortician so grimly satirized by Waugh in "The Loved One" may be interpreted as a form of denial of ageing and dying. But it is becoming an increasingly common feature of urban civilization in general issuing as it does from a scale of values which measures the worth of individuals in terms of their capacity to produce material wealth. This is not a setting likely to help those trying to adjust after a coronary thrombosis or treatment of a carcinoma, or those with failing faculties of whatever kind, to survive as integrated and functioning members of society.

Such adverse circumstances are likely to be partly responsible at any rate for the fact that 2% of the entire population of New York State (aged 65 and over) is resident in mental hospitals (Scheele, 1953) and that a fourfold increase was registered there between 1920 and 1942 in the rate of admission for arteriosclerotic psychosis (Pollock, 1945). A change of true incidence of this order is highly improbable. It must be due to a greater rate of admission of individuals who formerly managed to hold their own in the community.

The psychiatrist can do little beyond drawing attention to the evil effects of such trends. But the influence he can exert is enhanced when he can marshal precise data showing that the factors he holds responsible are in fact inimical to mental well-being. Our ignorance of the epidemiology of mental illness in old age is therefore a standing reproach. It is sixteen years since Faris and Dunham showed that patients with mental disease in senescence tend to come from the poor overcrowded and "hobo" areas of Chicago. To-day we know from

data issued by the Registrar-General (1955) that in this country the incidence of mental disease in old age is higher in urban than in rural districts and highest of all in greater London, and that individuals in social class V show twice their expected incidence of conditions loosely described as "senile and pre-senile psychosis" the other four having a deficiency of cases. But we know virtually nothing about the factors that govern such differences or about the ecology of the various types of mental disorder.

On the *biological* side we have to contend with the striking change in the expectation of life and in the pattern of causation of mortality in the last one hundred years. As wild mammals survive to manifest the stigmata of ageing only when protected in captivity from their natural predators, so we have begun to discover our full evolutionary heritage of degenerative disorder only since the advance of medicine has been disposing of our most dangerous enemies, the bacteria. And senile and arteriosclerotic psychoses, which cause much of the steeply rising incidence of mental disorder above the age of 65, represent a formidable part of the disabilities that have thus become an increasingly common hazard of existence. It would be wrong to regard such hazards as inevitable; adjectives such as "physiological" and "normal" confuse the issues before us and are a hindrance to research. These phenomena must be studied as diseases at any other time of life. But since we deal with processes to which we are probably all predisposed in one form or another it would seem likely that progress will have to await solution of some of the fundamental problems of ageing. In such a new field we have to be prepared to pick up clues from unexpected quarters. In this connexion, recent work on the commonest of the pre-senile psychoses, Alzheimer's disease, which almost certainly has some relationship to senile psychosis, is of particular interest. For it raises the possibility that such premature manifestation of cerebral ageing may result from some metabolic derangement that causes deposition of an amyloid-like substance in the brain to give rise to plaques, neurofibrils and vascular changes (Divry, 1947; Corsellis and Brierley, 1954).

With reference to Dr. Post's interesting idea that affective disorder in senescence may be a manifestation of some as yet unidentified form of ageing in the brain, there is certainly a lot of evidence for some special association between affective psychosis and old age. Thus, there is a peak in the incidence of affective psychosis as well as suicide in late middle or old age in most countries. And it is clear from the writings of other ages that the association between melancholia and senescence is no recent development. But on the assumption that those who become depressed for the first time in old age suffer from some subtle degenerative process in the brain, one would expect that it would require less in the way of stresses to precipitate the onset of illness; their incidence should therefore be smaller than in affective disorder that had commenced in earlier life. In fact the contrary is the case. First attacks of depression in old age are associated with a much higher incidence of physical illness than recurrences in senescence of depression in earlier life; the available evidence suggests that the physical disease has an important ætiological role (Roth and Kay, 1956). In women physical illness seems not quite so important, but there is a significant excess of widows among those having their first affective illness in old age, and the association between breakdown and bereavement seems impressively close (Kay and Roth, 1956). There is much to indicate that these patients are relatively stable people who break down only in the face of the most severe stresses and this is confirmed by the fact that their recoveries after treatment are more stable than those of patients who had also been ill in earlier life (Kay *et al.*, 1955). This would hardly be expected if some subtle cerebral atrophy were at all important in causation. I should also hesitate to contrast emotional ageing as in affective psychosis with intellectual ageing in senile psychosis, since the latter is always a global process that destroys all aspects of personality including affect and conation. However, the interesting suggestion Dr. Post has made certainly deserves to be followed up and more investigation should be devoted to the neuropathology of the functional as well as the organic groups of mental disorder in old age.

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Section of Obstetrics and Gynæcology

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DISCUSSION ON THE VALUE OF VAGINAL CYTOLOGY IN THE DIAGNOSIS OF CARCINOMA

Dr. J. Bamforth:

Malignant Disease of the Uterus

IT appears to me that at the present time the value of the cytological examination of the vaginal smear lies firstly in its use in preliminary diagnosis. Experience gained abroad and in this country shows that the cytological method possesses a considerable degree of accuracy in the diagnosis of carcinoma, and especially of the cervix. Graham (1953), working in Boston, stated that cancer cells were found in 423 of 469 cases of squamous-cell carcinoma of the cervix, an error of 9·7%. Other workers have claimed similar success and Anderson and his colleagues (1953) in Edinburgh showed an accuracy of 96·4% for cervical cancer. More false negative errors have been made by most workers in the cytological diagnosis of adenocarcinoma of the body, and I think that curettage of the uterus is preferable when carcinoma of the body is suspected.

In the great majority of cases the diagnosis of cancer of the cervix or of cancer of the body has been made in the past and can be made in the future without cytological examination. It is important, however, that many early and unsuspected cases of cancer have been brought to light by this method. By "unsuspected" cases one means those in which no biopsy would have been taken except for the positive report on the vaginal smear. The majority of such cases have proved to be carcinoma of the cervix and especially of intra-epithelial carcinoma, non-invasive cancer, or carcinoma in situ as this condition has been variously termed. It is the experience of most workers that relatively few cases of unsuspected carcinoma of the endometrium have been found. Anderson and his colleagues (1953), reporting on 3,000 cases screened for cancer of the cervix in Edinburgh found 33 unsuspected cases—an incidence of 1·1%. 19 of those proved to be non-invasive cancer, in only one of which was there any clinical suspicion of malignancy and in which a biopsy would have been done without the positive smear report. Only 1 unsuspected case of cancer of the endometrium was found but the technique employed was specially directed towards the diagnosis of cervical cancer. It is interesting to note that Wachtel and Plester (1952) in London found 7 unsuspected cases of carcinoma of the uterus in smears from 1853 cases; of these, 5 were carcinoma of the body and the other 2 carcinoma of the cervix.

The cytological changes found in squamous-cell carcinoma of the cervix cannot indicate whether it is invasive or non-invasive. In order to decide one must have recourse to biopsy and if necessary employ the method of serial section. It may be difficult, however, and in some cases impossible to decide where to take a biopsy. If a successful biopsy has been accomplished, the question of invasion may be difficult to determine. Such cases have been described as borderline. Furthermore, sometimes the lesion is multifocal in origin. The first case of intra-epithelial carcinoma of the cervix encountered by Dr. K. R. Dempster and myself proved on histological examination to possess three separate foci, one situated at an appreciable distance from the other two. Some gynæcologists employ a circular biopsy or conization of the cervix, a method which has been strongly recommended to deal with this difficulty. Unfortunately it has been found that conization does not always remove the whole of the diseased tissue.

What may eventually happen to these cases of intra-epithelial carcinoma of the cervix is problematical. There is no doubt that many of these cases progress to invasive cancer after a varying interval, sometimes after many years have elapsed. On the other hand, a perusal of the literature (and I would here mention a recent valuable paper by Petersen, 1955) shows that an increasing number of cases which have received no treatment have undergone complete regression. So far as I can ascertain there is no demonstrable histological difference between these two groups. There has been a tendency in many quarters during recent years not to employ the more radical methods of treatment but to adopt, especially in younger patients, a more conservative and watching attitude in the treatment of this condition and

to follow it up with repeated biopsies if indicated. It is here that cytology can play an important part. It has been shown that the vaginal smear is extremely accurate in detecting local recurrence in carcinoma of the cervix even before it can be recognized clinically.

Secondly, therefore, the examination of the vaginal smear is of great value as an aid to the observation of the progress of a diagnosed intra-epithelial carcinoma of the cervix when radical treatment is not primarily instituted and in the follow-up of cases of invasive cancer of the cervix treated by irradiation or surgery or both from the outset.

Lastly, it has been claimed that cytological examination of the vaginal smear is a useful guide in prognosis in the treatment of cancer of the cervix by radiation. Certain changes in the non-malignant epithelial cells are brought about by radiation and it is claimed that a rise in the percentage of these benign irradiated cells is of good prognosis. Of this I have little experience.

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Dr. G. R. Osborn:

We use vaginal cytology whenever the gynæcologist thinks it indicated, this is about 1,500 times each year. With relatively few exceptions it is not an isolated investigation but part of a full examination. To help determine its value I have studied the findings in 311 cases of carcinoma of the uterus seen in the five-year period 1950–1954.

Carcinoma of the body is not a rare disease nor does it fail to reveal its presence in most cases cytologically. 129 cancers were in the body. 63 of these had pre-operative cytology which suggested or gave the diagnosis in 46, there were 17 "false negatives". 44 women had preliminary biopsy only, and 22 were diagnosed at operation or from the operation specimen. 6 of the recurrences after treatment were first diagnosed cytologically. Although this is an adenocarcinoma we do not see glandular structures in the smears, the cells appear singly or in papillary processes. In the very well-differentiated growths the distinction from endometrial cells can be difficult. This rests on minor degrees of nuclear variation, double nucleated forms, and especially on the presence of mitotic figures which have never been seen in endometrial cells shed naturally. The processes with mitotic figures were obviously alive at the time of collection, I consider them the source of the "seedling implants" which may be found in the cervix, vagina or tubes at a considerable distance from the primary tumour.

182 had carcinoma of the cervix. 116 of these had pre-treatment cytology. The diagnosis was suggested or made in 93, there were 23 "false negatives". In 34 cases there was a preliminary biopsy only, 32 were first proved from the operation specimen. 10 recurrences after treatment were recognized cytologically. These recurrences of the squamous cell carcinomata had not been appreciated before the review was made, probably for two reasons: (1) The operation specimen after radiotherapy typically shows complete destruction of normal and malignant epithelium in the region, the recurrence or residual disease is at a distance. (2) Less interest had been taken in them because the cells desquamated are not considered viable and capable of producing "seedling implants". Cytology is not able to distinguish between an invasive and a pre-invasive carcinoma; it is not always able to distinguish between an adenocarcinoma and a squamous cell growth.

47 cases of carcinoma-in-situ have been studied over a rather longer period. Their average age is 41, the range 28–72 years. For invasive squamous cell carcinomata the average age for 150 cases was found to be 54, and the range 27–83 years. Nearly all observers have shown that the average age of the woman with carcinoma-in-situ is 10 years or so less than the average for those with invasive growths of the cervix. This fact, and direct observation, are the reasons for believing that carcinoma-in-situ may exist for about ten years before giving rise to an invasive tumour. As in cancers elsewhere we are never safe in applying this knowledge of group behaviour to any individual case, it will be noted that the youngest woman with an invasive cancer of the cervix was one year younger than the youngest with a carcinoma-in-situ. If we say that carcinoma-in-situ is not likely to become invasive for ten years we are bothered by not knowing when the ten-year period began. Of the 47 cases 42 had pre-treatment cytology, in 30 it was positive, there were 12 "false negatives". 5 of the false negatives were in the transitional stage of basal hyperplasia to carcinoma-in-situ. 2 cases were in the cervical stump after subtotal hysterectomy. 31 of these women have been treated by hysterectomy, 5 by radium and 11 are under observation. Before giving treatment, especially to the younger women, it is evident that the gynæcologists

now require cytology confirmed by histology, or histology confirmed by cytology, often on many occasions. A number of lessons have been learned: (1) Cytology never makes a diagnosis of carcinoma-in-situ, it just indicates the presence of a malignant tumour of some sort. (2) Biopsy confirmed by cytology only makes the diagnosis of pre-invasive carcinoma a probability; there may be an invasive growth in a part from which the biopsy has not been taken. (3) Especially in its early stages carcinoma-in-situ may be a very small lesion, so small that the cytodiagnosis may be hard to confirm histologically, these are the cases most suitable for observation. Mitotic activity is so prominent in the typical carcinoma-in-situ that it performs its own "concentration test" for the cytologist, if these cells did not desquamate so freely a massive lesion would be produced much more rapidly than it is. (4) Too much attention has been paid to these microscopic lesions and not nearly enough to the commoner extensive form, it is common to find it over most of the cervix and some of the vagina; in a woman aged 70 it covered all the cervix, extended over the senile endometrium to the fundus, and infiltrated beyond the line of division in the vagina so that smears after hysterectomy were still positive. Before operation an attempt should be made to determine the extent of the disease. (5) Experience indicates that carcinoma-in-situ is appreciably commoner in women who have some reason for attending the gynæcologist, e.g. for sterility, than it is in normal women who attend a "cancer prevention clinic". (6) Although pregnancy increases the malignancy of most forms of cancer it does not appear to hasten the transition from the pre-invasive to the invasive form of squamous carcinoma. Provided all facilities are available for observation selected women may be allowed to continue to full term and even allowed a subsequent pregnancy; this is never devoid of risk but with full investigation the risk is so small as to be justified. (7) If conservative operative treatment is given for carcinoma-in-situ raw surfaces should be left to heal by granulation and not epithelialized, this will enable the patient to be followed cytologically.

The 40 "false negative" cytodiagnoses have been reviewed. 18 of these are good smears which are quite negative, i.e. 10%. Experience of other cases leaves little doubt that this 10% would have been appreciably less had more than one cytological examination been made. Some false negative reports are, however, unavoidable e.g. one woman with an obvious carcinoma of the endocervix had negative smears on six successive days. Of the remaining 22 cases 13 smears were too scanty for diagnosis, 8 proved to be "suspicious" but far from diagnostic, and 1 was a positive, missed because of good differentiation. Some of the lessons learned about false negative cases are: (1) Because some smears are taken badly about 20% of the cases of cancer have negative cytology. If all smears were taken well this figure would fall to 10%. If all women with cancer of the uterus had more than one cytological investigation the figure would probably fall to about 5% but cytological investigation alone will not eliminate all false negatives. (2) Because cytological investigation preceded histological in the proportion of 7 to 1 these false negatives could have been serious, fortunately this did not prove to be the case because they were mostly recognized quite quickly by other diagnostic methods. (3) If cytological investigations were available to all general practitioners most women with cancer of the uterus would be brought to treatment earlier but the problem of the false negative would become more serious. (4) The notes indicate that infection with *Trichomonas vaginalis* can be mistaken clinically for cancer, and that a cancer can be overlooked because of this infection. Because we find the cytological method gives 50% more diagnoses than the wet smear, and that the positives are very much more positive, we have abandoned methods other than the stained smear for the diagnosis of *Trichomonas vaginalis* infection. The experienced observer recognizes this protozoon so quickly and in such vast numbers that there is a risk of an inadequate examination for cancer cells. Fortunately the obvious infection with this parasite only resulted in one woman (aged 39) being treated conservatively (for 13 months) after a cytological diagnosis of cancer had been made. (5) A heavy purulent discharge in a woman aged 57 with pulmonary tuberculosis caused the clinician to doubt the cytological diagnosis of cancer for eleven months before it was proved by biopsy. (6) The greatest cytological difficulty has proved to be the smear which is "too good to be true"; these have mostly been from very well-differentiated adenocarcinomata, the numerous cell clusters from which resembled either endometrial cells or histiocytes. One such smear came from an unusual small-celled squamous cell carcinoma of the cervix—yet another instance of the danger of attempting to take a cytological diagnosis too far, the smear certainly indicating an adenocarcinoma of the body. (7) Suspicious smears which are not diagnostic can be followed up in the gynæcological department without the serious psychological effects sometimes seen in the "cancer prevention clinic". Provided the gynæcologist knows the pathologist is giving very few false positive reports this should be done; in the case of a woman aged 31 there was only one cluster of cancer cells so a definite report was not made, histological confirmation was therefore delayed ten and a half months.

False positive reports should not occur, probably a few are inevitable but if they exceed

5% diagnostic criteria must be reviewed. The most fertile sources of error are histiocytes, squamous metaplasia and endometrial cells. I find that I do not confuse endometrial cells with cancer cells but there is a risk of calling the cells from a well-differentiated adenocarcinoma endometrial cells.

It is not difficult to demonstrate the presence or absence of "radiation response" cytologically and histologically. Far too many of these observations have failed to correspond with the findings at radical hysterectomy for me to be satisfied the method is sound. For unknown reasons the sensitivity in some carcinomata varies in different parts, in one there was a good histological "radiation response" near the cavity and peritoneum but not in the central parts.

Conclusions.—(1) Cytology is an essential part of most gynæcological investigations. (2) To the pathologist it is the most interesting branch of cytology because its value is not confined to the diagnosis of cancer. Cytological investigations are more rewarding and less time-consuming than many investigations regarded as essential in other sections of the general pathological laboratory. (3) Possibly the greatest value of cytodiagnosis is that it can recognize carcinoma-in-situ as easily as advanced invasive cancer in most cases. (4) The occurrence of cancer cells in the smear does not appear to depend on whether the cancer is obvious clinically or not. Hence very few cases of cancer will be missed if both histology and cytology are used; either may be negative but it is improbable that both will be. (5) Vaginal cytology alone is certain to miss about 10% of the cancers of the uterus. Various scrape methods have been introduced to overcome this. We obtain better results by histological processing of superficial cervical curettings removed with a Volkmann's spoon and think this should become a standard diagnostic method. Especially in the young woman complaining of sterility it should be done before thinking of a ring or cone biopsy. (6) Until radical treatment is given carcinoma-in-situ must be followed up cytologically. If conservative treatment is given raw surfaces must not be epithelialized so that a cytological follow-up will be possible. (7) There will be very few false-positive cytology reports if the observer is well trained. (8) To assist the training of the cytologist and the complete study of cancer of the uterus the gynæcologist should take smears from all cases—not omitting those where the diagnosis is quite obvious without cytology. (9) Some women operated on for very obvious conditions, e.g. fibroids, also have an unsuspected carcinoma, sometimes the operation would have been more extensive had this been known. Routine pre-operative cytology in such cases would be a simple and profitable investigation.

Mr. A. J. Wrigley:

The cytological examination of sputum, urine and other secretions of the body for the presence of cancer cells, has been practised now for at least thirty years. As early as 1927 the late Professor L. S. Dudgeon and C. V. Patrick published a description of their work entitled "A New Method for the Microscopical Diagnosis of Tumours" which was followed shortly by a similar account by Dudgeon and Barrett (1934) of the continuation of this work. In 1932, under the inspiration and supervision of Dudgeon, the method of cytological examination was extended to gynæcology and another paper appeared from the St. Thomas's group (Wrigley, 1932). I mention this because it is widely and inaccurately assumed that the whole credit for the initiation of cytological investigations in the diagnosis of malignant disease originated from the Northern Continent of America.

It is true that as early as 1928 Papanicolaou had discovered cancer cells in the human vaginal smear and that certainly Papanicolaou (1928) and later Ayre (1949) and others were responsible for the large-scale development and assessment of the smear technique. Nevertheless, equally valuable and similar work was being done in this country certainly parallel, if not taking precedence, to that in America.

For practical purposes, and in this country at any rate, no volume of work on the vaginal smear technique was performed before the end of the war, ten years ago, and for the most part this work was limited to very few centres. The reasons for this were fairly obvious because the obtaining of the specimens, their interpretation by the cytologist, and the methodical recording of results, necessitated a team of workers who were prepared to devote a considerable amount of time to these initial investigations. In addition, it was soon discovered that not every pathologist was a cytologist, and that accurate and knowledgeable observers of the changes in cell structure were few, very few, and far between and that their training was likely to be lengthy and arduous. Nevertheless, such workers can be trained, though from my observations their training is most likely to be successful if it is tackled by a process of prolonged infiltration rather than by the much more popular concentrated course of study in a "Cytological Laboratory".

To-day vaginal smears are being made with varying intensity and enthusiasm in many

different parts of the country. The poor clinician, who is seldom a member of such a team, is rather left to his thoughts, which may be summarized at this point:

(*a*) How accurate is this method in the diagnosis of cervical and corporeal cancer?

(*b*) Which patients in a hospital out-patient clinic ought to be examined by the smear technique?

(*c*) Of what help is the vaginal smear likely to be to the general practitioner?

(*d*) Can its value be extended to any purpose other than the initial diagnosis of cancer?

(*a*) *The accuracy of the cervical and vaginal smear.*—In the last decade a number of mass investigations of the smear technique have been performed in the North American continent and in some instances (Cuyler *et al.*, 1951; Graham and Meigs, 1949; Nieburgs and Pund, 1950; Skapier, 1949*b*) tens of thousands of women have been examined. In the majority of such series accuracy of the results by no means varies according to the numbers of patients examined. The statement that the commonest error made in the diagnosis of carcinoma of the cervix is the false positive is repeatedly shown to be correct. Thus Nieburgs and Pund (1950) found this to be so in 21% of their cases diagnosed as Stage 1 cancer. Kraushaar *et al.* (1949) discovered 191 cases of cancer out of 5,314 investigated and subsequent biopsy confirmed only 100 of these results. Nevertheless, the smear probably is more accurate than the biopsy in cases of early carcinoma, for Ruth Graham and Joe Meigs (1949) out of 40 cases of proved carcinoma-in-situ demonstrated the smear to be correct in 35 and biopsy in 28. August F. Daro (1953) similarly found that in early cases of cancer of the cervix, the punch biopsy of the cervix had an error of 9·3% whereas in the smear technique the error was only half, 4·6%, that figure. When the two methods were combined, and I will refer to this when we consider our conclusions, the resultant error rate was reduced to 1·7%.

It is probable that A. F. Anderson and his colleagues (1953) have presented us with the most fair and true picture of the accuracy of the technique when, out of a series of 3,000 cervical smears, they recorded 4 cases of cancer missed out of the first 1,000 patients examined and only 1 case missed out of the next 2,000. They noted only one false positive.

The picture in relation to corporeal carcinoma is entirely different. Anderson *et al.* (1953) observed that over 50% of 21 cases of proved cancer of the body of the uterus were missed, and confirmed the opinion of Douglas M. Haynes *et al.* (1952) and many others. In this type of growth mention must be made of the recent work of E. Lawrence Hecht (1953) whose results with what he terms the aspiration smear seem to be much more encouraging. He records 3 cases in which the technique made an accurate diagnosis, when curettage had already failed to demonstrate the presence of carcinoma.

We may conclude therefore that, given the services of an experienced cytologist, the cervical and vaginal smear technique is remarkably accurate, especially so in the diagnosis of early cases of cancer of the cervix.

(*b*) *The scope of investigations by the smear technique.*—If we accept the accuracy of the technique, we may well ask ourselves whether every woman should not be so examined at regular intervals throughout her life, and more frequently during the fifth decade. Such thought far from being original has already been put into practice. Thus A. F. Anderson found entirely unsuspected cancer in 1·1% of cases which were not entirely unselected. Skapier (1949*b*) found 30 cases of cancer in 10,000 women examined and this figure probably fairly represents what we may discover in any mass investigation made at any one time.

I would say, in regard to the question of population "screening", that it may be more favourably received in some parts of the world than in others. I would further suggest we ask ourselves whether we would save more lives by the early diagnosis of unsuspected, usually intra-epithelial Stage O, cancer than we should lose by the small but inevitable mortality that accompanies hysterectomy. Now is a good time to mention the cost of these mass investigations. This has been variously estimated at $150 (£60) by Nieburgs and Pund (1950), $357 (£125) by Douglas M. Haynes *et al.* (1952) and at over £500, I believe, by Stanley Way, per single diagnosis of unsuspected cancer. I am not perturbed by this particular item, for I would believe him to be a brave man who would assess the monetary value of a mother of a family at £500 or less. There are many other points both for and against such mass investigations, but I think we may summarize by saying that for us in this country the time is not ripe.

I would, however, suggest that the routine use of the smear technique in patients with symptoms or signs, both in the Out-patient Clinic and in General Practice, is an entirely different matter. Thus Skapier (1949*a*) found the incidence of positive smears was 1 in 354 out of 8,000 symptomatic cases examined. In a similar series examined by Graham and Meigs (1949) the incidence was 1 in 200, which figure coincides with the findings of A. F. Anderson *et al.* (1953).

If we consider results such as these and if in addition we accept that a high degree of accuracy exists in the smear technique for the diagnosis of early cancer of the cervix, the clinician is very naturally confused by the consistently repeated advice that the smear results must be confirmed by biopsy (Lock and Caldwell, 1949; Ayre, 1949; Graham and Meigs, 1949; Greenhill, 1950) and that under no circumstances must definite therapy be undertaken on the basis of the smear alone (Haynes *et al.*, 1952). The argument is most reasonably put forward in such words as these: "If I find in any patient symptoms or signs that may suggest a possible malignant lesion in the cervix, what is the object of making a vaginal or cervical smear, when in any case, apart from my own judgment, I am advised by the smear enthusiasts that a biopsy must be performed for confirmation? Is it not waste of my time and of the pathologist's time?" This is all very well up to a point, but I am sure that in such selected cases we should continue to use the smear technique as part of our examination for the following reasons: Firstly, our knowledge on this matter is far from complete and we are supplying valuable material for a valuable piece of research into a possible means of early diagnosis of cancer. In the second place, as stated by Ruth Graham and Meigs (1949) "a real advantage of the cytolic method is that the diagnostic accuracy is greater in early than in far advanced carcinomas and that the region examined is not limited in size and location" as is the case of the ring or punch biopsy. These two points are of very great importance as we are always coming across, and more frequently reading of in the experience of others, instances in which the positive smear is followed by a negative biopsy, which when repeated shows the smear to be correct. That no therapeutic action should be taken on the smear report alone I am sure no one will disagree. Therefore, I would advise that there be no diminution in our use of, or enthusiasm for, this method of investigation.

Ayre and others have shown how the Papanicolaou technique can be extended to general practice, and used therein to the greatest possible extent. I believe every practitioner should continue to send to hospital any and every patient in whom, from symptoms or signs, cancer of the cervix might be suspected. There is, however, another and large group of women whose doctor feels that while the ordeal of a visit to the Gynæcological Department of a hospital is really not necessary, at the same time wishes that his opinion could be fortified by some confirmatory investigation. I consider this point to be of great importance. The making of a satisfactory smear can be performed by any practitioner with slight instruction and Ayre has shown how it is possible to organize a country-wide service for the examination of these preparations. There is no reason against, and every argument for, a repeated examination at a later date if the doctor remains at all dissatisfied.

The last question asks whether the technique can be of use in any respect other than in the diagnosis of malignant disease. Already it has proved most valuable in the estimation of the response to treatment of carcinoma with radium and as a routine investigation in the follow-up of such cases following treatment by surgery or by radiotherapy.

Ruth Graham and Meigs (1949), Ruth Graham (1951) and John B. Graham and Mesig (1952) have demonstrated these two points and have made the following observations: In the case of a patient who is being treated by means of radium and X-rays regular observations should be made during the period of treatment on the changes in the cell picture and structure. A marked reaction indicates a probable favourable response to the treatment whereas a poor reaction is likely to be followed by no beneficial changes in the tumour. Thus Graham and Meigs (1949) in a study of 73 cases treated by radiotherapy were able to show that examination of the smear picture as an index to prognosis was at least 75% accurate. Of 37 patients in whom a poor response was noted in this manner only 1 was alive and well at the end of five years, while out of 26 others in whom the response to treatment was good no fewer than 23 were well at the end of the same period. A poor response observed during treatment by radiotherapy might well lead to further consideration as to the advisability of treatment by radical surgery and such a decision made at an earlier date could be greatly to the advantage of the patient.

The presence of malignant cells, demonstrated in smear preparations made three months after the completion of treatment by radiotherapy would be a grave indication that such treatment was unlikely to be successful, while such a finding three months later could be taken that treatment was ineffective. Similarly a positive smear found following surgical removal indicates the failure to eradicate the disease, while if a positive smear is discovered in such a patient following repeated negative findings it can be concluded that the tumour has begun to grow again. These conclusions may appear obvious, but their importance lies in the fact that this cytological method of diagnosing the presence of cancer cells enables the recognition of recurrence *long* before it becomes obvious clinically. This examination must be an essential at every routine visit in the follow-up of every case of treated cancer. As a result this may lead to a modification of the present line of treatment or to instigation of

further and different therapy. It is quite certain that there is scope for additional and valuable work on these matters.

I would offer the following conclusions:

(1) We accept the accuracy of the Papanicolaou smear method of diagnosis of early cancer of the cervix.

(2) We are not to-day prepared to advocate the routine examination of all women by this method.

(3) We do not advise the examination of all patients attending gynæcological clinics by this smear technique, except when some special research is contemplated.

(4) We do believe that the examination by the vaginal and cervical smear should continue, and be encouraged, both in gynæcological clinics and in general practice, in all patients who present symptoms or signs of possible early carcinoma of the cervix, and we advise the continuation in all such patients of the old-established methods of diagnosis by biopsy and curettage.

The use of the two methods concurrently must not be regarded as unnecessary and as a waste of time for each would appear to possess advantage over the other under certain circumstances and we have seen that the two combined can greatly diminish the risk of failure to establish the presence of early disease.

(5) Lastly, we recognize that further work can be done by use of the smear technique in respect of the response to treatment by radiotherapy and in the detection of recurrence following any treatment, with an appreciation of the possible benefit this may have on the nature of final or additional therapy.

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Professor Hugh McLaren:

Regarding the incidence of post-coital bleeding, the figures I gave you are correct, namely 3% in ordinary out-patients and 16% if the patient is specially asked. What was not clear, however, was that this incidence of post-coital bleeding referred not to the general run of out-patients but only patients admitted to hospital for suspicious symptoms such as post-menopausal bleeding, intermenstrual bleeding, post-coital loss and so on. The total number of cases, admitted from our series was 254, i.e. about 10% of all out-patients. The true incidence of post-coital bleeding is, therefore, not yet clear from our studies but I imagine that if "every" patient were asked the incidence would be about 2%.

May I make a plea for the abolition of the term "cytological diagnosis"? In fact, no cytologist makes a diagnosis. The positive smear is placed alongside the clinical facts and histological reports. Finally a joint diagnosis is made and a joint decision on further investigation or treatment is reached by the whole clinical team including the cytologist. This close liaison between the members of the team is necessary not only for research but in order to integrate correctly the technique of cytology into gynæcological practice giving the technique no more than its due place as a laboratory test of considerable importance.

I should like to plead for an exact definition of the term "cytological pick-up" or as we prefer to call it in Birmingham the "surprise positive smear" which is finally confirmed as having its origin in carcinoma of the uterine body or cervix or carcinoma-in-situ of the cervix. Too often in the literature the term "pick-up" rate is given as "*x* cases per 1,000" without a clear definition of the quality of the clinical screen through which the patient has passed. We found ourselves in difficulty after our first 800 cases. Vital questions were missing from our original outpatient notes such as reference to post-coital bleeding which, of course, is a very suspicious symptom. Again, too often the description of the cervix was sketchy or incomplete. In order to define exactly what was, in fact, a "pick-up" to be credited to the technique of cytology we found ourselves compelled to design a special set of questions applicable to every out-patient. This had the effect of compelling the clinician to ask certain questions and to record exactly certain observations and finally to compel him to write down clearly at the end of his case-notes whether or not in his opinion the patient had carcinoma of the cervix or uterine body. Added to this, of course, were the notes of patients admitted to hospital for curettage and perhaps a ring biopsy of the cervix. Once again if the clinician failed to make a diagnosis by routine clinical (in-patient) methods a true "pick-up" could be accredited to the cytological technique, provided, of course, reassessment of the case confirmed the fact that the cells described by the cytologist had, in fact, their origin in carcinoma of carcinoma-in-situ.

The problem can be put in another way by asking ourselves how many cases of cancer or carcinoma-in-situ may a clinician expect to miss in his gynæcological practice without cytology. This figure is a very variable one in reports from various centres working in this field and the true interpretation of the "pick-up rate" is often very difficult. A standard definition such as we have outlined might be acceptable to other workers and would certainly make it easy for figures from different centres to be compared.

[*January* 27, 1956]

The Place of Myomectomy in the Treatment of Primary Infertility

PRESIDENT'S ADDRESS

By GERTRUDE DEARNLEY, M.D., F.R.C.O.G.

Introduction.—I am venturing to present a series of cases of abdominal myomectomy done primarily for the cure of infertility.

Myomectomy has for many years been the operation of choice in the removal of myomata for hæmorrhage or other symptoms in patients under 40 years of age. Where a smallish myoma is present in the uterus and causing no symptoms, the general opinion has been that the best course is to do nothing, unless any change in size is observed.

Review of the literature.—There are widely differing opinions as to the part played by myomata in the causation of sub-fertility. Hofmeier (1913) claimed that myomata play no part in the causation of sterility but are merely associated with it as part of a constitutional disease. Olshausen (1898) found an incidence of 30% sterility in 1731 married women with myomata. Douglas (1948) in a study of sterility as related to benign lesions of the uterus and ovary, asks whether sterility is the primary affection with the genesis and development of myoma as a consequence, or whether the two are a common symptom of some hormonal or constitutional disturbance. In his opinion the connexion between the two is still an unsolved problem, but proof that fibroids are sometimes the cause of sterility is apparently seen in women who promptly become pregnant following a myomectomy.

If it is granted that myomata play a significant role in the causation of subfertility, the next questions to be considered are the exact indications and results of operation. One great difficulty in the investigation of this question is that very few of the published statistics take account of the position of the woman as regards age, marital state, and desire to have children. Massabuau and Guibal (1933), in the course of an extensive review, give some figures which show the great variation which may be expected in the results of myomectomy; these authors record a total of 192 pregnancies following 2,916 myomectomies (6%). The incomplete nature of most series of cases gives special interest to Goullioud's (1929) figures of 27 pregnancies in 100 women in whom conditions were suitable for conception. Giles (1923), one of the earliest British advocates of conservative operation, reported two series of cases with a grand total of 49 women who had a chance of conceiving after operation and

of whom 13 (26%) became pregnant. Banister (1927) reported 6 cases in which the only complaint was sterility and in which pregnancy followed in every case after myomectomy.

Sir Arthur Gemmell (1936) in his survey made every effort to ascertain the number of patients likely to become pregnant. This figure was 523 and of these 145 conceived (27·7%). Of the patients who did become pregnant 128 gave birth to 133 living children; there were 17 premature labours and abortions and 9 abnormal labours of which 3 were possibly due to myomectomy. He adds that all the factors concerned in sterility are not analysed in the published papers; but if, as appears, approximately one-quarter of the patients treated for fibroids later conceive, it is worth striving for such a result. Gemmell notes that some patients themselves nullify the efforts of the gynæcologist: 12 patients in the Liverpool series are known to have practised contraception. In connexion with the fear of possible complications during labour it is of interest that Benoit-Gonin (1913) could find only three cases of rupture of the uterus in the literature.

Cotte and Magnin (1939*a*) report a series of 40 cases in which pregnancy followed 16 times. Of these 13 went to term and resulted in living children, while 3 terminated in miscarriage. The same authors reported (1939*b*) on 41 married women, all under 41 years of age at the time of operation, in whom there was no gynæcological condition which could be regarded as an obstacle to pregnancy, apart from the presence of uterine myoma. Two of the patients operated upon said thay had no desire for children. Of the 33 remaining, 10 became pregnant after myomectomy. Hamant (1933) reported 188 myomectomies resulting in 35 pregnancies; 22 of his patients had one pregnancy, 7 had 2, 4 had 3, 2 had 4.

The largest personal series reported in this country is that of Victor Bonney (1937). He followed-up 370 patients upon whom he had operated up to 1933. Of this total there were 137 who, being married and within the child-bearing age, desired children. Of these 52 conceived after the operation (38%). Natural delivery ensued 34 times, Cæsarean section was performed 17 times, and there was one miscarriage. These figures record only the pregnancies first occurring after the operation.

Mussey *et al.* (1945) published a review of 250 cases in which myomectomy was performed. In all of the selected cases the patients had been married more than three years and previously had not received treatment which would affect their fertility. In 82 of the 221 cases in which the patients were not pregnant when myomectomy was performed, there was a history of infertility prior to the operation. 8 of the patients subsequently conceived and gave birth to a total of 11 living children. 101 of the 250 patients became pregnant 167 times after myomectomy and there were 128 surviving infants. Novak (1945), in the discussion on this paper said he believed that myomectomy is not infrequently indicated in the case of young women who are extremely anxious for children and in whom careful study has apparently eliminated other causes of sterility. "Anyone who has carried out this procedure in any great number of cases must have been impressed with the considerable proportion of successes which it yields, pregnancy often occurring rather promptly after operation following even years of sterility."

Rubin (1952) had 73 personal cases in which sterility was associated with fibroids and in which myomectomy was performed; pregnancy was produced in 21 (28·9%) and 15 had children at term. This author cites Engstrom as curing sterility in 26·4% of cases, Essen Moller in 10%, Hunner in 27% and Polak in 33%.

Jones (1953) reported his experiences with myomectomy in 56 cases. 11 women bore from 1 to 4 children following the operation. This author recommends the procedure as a means of salvaging the uterus for its normal functional purposes. He refers to the possibility of tumour recurrences but in his opinion the slowness of growth of the tumours will permit the uterus to function normally for several years after the operation. This period is ample for one or two pregnancies to develop and be successfully concluded.

Royal Free Hospital.—During the war, as there was less maternity work in London, I turned my attention to the study in more detail of the operative procedures which are beneficial in the treatment of infertility. As we had fairly recently started an infertility clinic at the Royal Free Hospital these operations fell largely to me. I became very interested in this aspect of treatment and was much encouraged by the successes which were obtained.

In some of the cases I was reluctant to do abdominal myomectomy where many fibroids were present and the patient's age in the late thirties. I was, however, greatly encouraged by cases such as that of Mrs. A., aged 34, whom I thought hopeless, but who subsequently had two children. I began to do more myomectomies where the only complaint was infertility and where the myoma often small appeared to be causing no symptoms otherwise. The results were often so striking that I became converted to what I believe is good treatment in such cases.

Selection and classification of cases.—This series is not large as I have limited myself to married patients in whom sterility was the main complaint, associated in some cases with menorrhagia or dysmenorrhœa.

This group of cases has been collected by examining the Hospital records for the past fifteen years and by including some private patients. I have included patients in whom a miscarriage had occurred previously, but not patients who had had a child before coming for treatment of sterility. We sent out 113 questionnaires: 24 failed to reply and a further 9 were not included because after the operation they decided they did not want a child. The 80 replies, which form the basis for the present study, all relate to married women who desired children and came to us for the treatment of sterility.

This series may be a selected group as it is possible that patients who have had a child as result of operation are more inclined to reply; but although the figures may not be considered adequate for statistical purposes, they may be of interest as a basis for future work.

In most of the patients operated upon from the infertility clinic the fertility or otherwise of the husband was known, but in some of the other cases could not be ascertained. Investigation into the patency of the tubes and other tests together with a general examination was carried out before operation. All these patients were anxious to have children.

The total number of cases in which nothing abnormal except myomata was found on clinical examination is 56. I have divided these into three groups:

I. Myomectomy only performed	36 cases
II. Myomectomy with dilation and curetting	12 cases
III. Myomectomy with shortening of the round ligaments ..	8 cases

GROUP I.—36 *Cases of Primary Sterility Treated by Abdominal Myomectomy*

In this group of cases the patient complained of sterility and the only abnormality to be demonstrated was a myomatous condition of the uterus.

6 of these patients had a miscarriage before myomectomy.

Average age at time of operation	34 years
Average time married	4 years 2 months
Average time after operation to birth of first child ..	1 year 9 months

1 patient had 3 children following operation
6 patients „ 2 „ „ „
12 „ „ 1 child „ „
3 „ „ miscarriage after operation

22 patients became pregnant. 14 failed to conceive. A total of 27 children were born full time.

1 patient had Cæsarean section for first child after twenty-four hours trial labour. The uterus showed no signs of the previous operation at which six fibroids had been removed. A set Cæsarean was performed for the second child (weighing 10 lb.) and the patient was sterilized. A second patient had Cæsarean section for a 6 lb. 14 oz. baby on account of placenta prævia. No signs of myomata were seen in the uterus.

1 patient had one normal delivery at full term. The doctor advised no further pregnancy as he suspected the presence of myomata.

In 2 patients, each of whom had one child after myomectomy, hysterectomy was performed for hæmorrhage four and seven years after the primary operation respectively.

1 patient had a myomectomy in 1943 but no children; hysterectomy for hæmorrhage in 1950.

1 patient decided against pregnancy one year after operation; husband subfertile.

Pathology.—Of the 22 patients who became pregnant 9 had a single myoma which varied in size; 13 had multiple myomata large and small.

Simple myomata without degeneration were found in 14 cases: 10 showed hyaline degeneration, 2 necrosis, and 2 cellular change. No malignant changes were observed in any cases in this group. In 10 cases pathological reports could not be found.

No operation was performed on ovaries or tubes in these cases.

GROUP II.—12 *Patients Treated by Myomectomy and Dilatation and Curetting*

The chief uses of dilatation and curettage are to get a biopsy of the endometrium so as to ascertain its functioning and also to exclude malignancy. It has not been my custom to do this as a routine.

Average age at time of operation .. .. 35 years 4 months
Two patients in this group aged 41.
Average time married .. .. 4 years 4 months
" " between operation and birth of first child .. 1 year 11 months

Patients
8 became pregnant
1 has had 2 full time children since operation.
3 have had 1 full-time child since operation.
(One of these patients aged 41.)
1 is now 5 months pregnant.
1 had 2 miscarriages followed by hysterectomy for recurrence at age 28 years (not by me).
1 had 4 months miscarriage after skating accident and her doctor advised no further pregnancies.
1 had ectopic pregnancy.

Of the 4 patients who failed to become pregnant 1 (aged 27) abandoned attempts to conceive six months after operation.

5 husbands in this group were subfertile.

Pathology.—1 showed mild obvious inflammation including degenerate scraps of decidua. This patient had a three months' miscarriage some months before operation; she subsequently had a full time child.

The *curettings were normal* but for 3 which showed persistent proliferative phase; one of these developed ectopic pregnancy; two did not become pregnant.

2 patients had complained of discharge; 1 of these had two children after operation.
Multiple myomata in 10 cases. } No malignancy.
Single myoma in 2 cases. }
Hyaline degeneration of myomata in 4 cases.
Necrosis of myomata in 2 cases.
All were simple fibromyomata.

GROUP III.—8 *Cases of Myomectomy with Shortening of Round Ligaments*

In some cases where the uterus is retroverted before operation or where after myomectomy the uterus is very low in the pelvis, it is an advantage to raise the uterus into a higher anteverted position by means of a Gilliam's suspension. It is thus I believe in a more advantageous position for becoming pregnant.

A total of 8 patients had myomectomy and a modified Gilliam's operation, and only 1 failed to conceive.

4 patients also had dilatation and curetting.

Average age at time of operation .. .. 31 years 8 months
Average time married .. .. 5 years 6 months
" " between operation and birth of first child .. 1 year 11 months

Patients
6 had 1 child at full term following operation.
1 had a miscarriage.
5 had a retroverted uterus associated with myomata.
3 had an upright or anteverted uterus before operation.

Pathology.—Multiple myomata present in 5 cases. Single myoma present in 3 cases. All simple myomata with hyaline degeneration in 4 cases, 3 with no degeneration (1 patient: no pathological report).

Curettings.—Carried out on 4 patients. 2 showed persistent proliferative phase. Both bore children. 2 miscarriages—nil abnormal.

OVERALL RESULTS IN GROUPS I–III. OF THE 56 CASES IN THE 3 GROUPS

Total number of cases of abdominal myomectomy alone	36
Total number of cases of abdominal myomectomy with D and C	12
Total number of cases of abdominal myomectomy with modified Gilliam's operation (with 4 cases also having D and C)	8
Total	56

1 patient had 3 children } 38 full time children
7 patients had 2 children }
21 patients had 1 child }
1 patient now 5 months pregnant

Therefore 29 patients out of the 56 had full-time children.

GROUP IV.—24 *Cases of Myomectomy associated with Operation on Tubes or Ovaries for Various Lesions*

It is well known that cystic diseases of the ovaries and endometriosis are frequently associated with infertility and that these conditions are often found with myomata. Any lesion of the tubes is also unfavourable. In these cases operative procedures give very poor results.

In this series of 80 women complaining chiefly of sterility, the condition was found at operation in most of the cases, but in only 13 of 24 had this complication been diagnosed or suspected beforehand.

Huber (1939) made a study of 432 myoma cases which included systematic histological examination. In his opinion the most frequent cause of sterility in the presence of myoma is endometriosis of the tube, a finding present in more than half of his cases. He states that endometriosis was far more frequently associated with multiple myomata than with single myoma (69·6% and 33·3%). In my series of 24 cases 12 patients had multiple myomata and 12 had a single myoma.

(Royal Free Hospital Cases)

Average age at time of operation 34 years 6 months.
Average time married 5 years 4 months.

10 patients complained only of sterility; no change in menstrual period
8 complained of sterility plus increased menstrual loss
3 complained of sterility plus increasing dysmenorrhœa
2 complained of sterility plus increase in menstrual loss plus increasing dysmenorrhœa
1 complained of sterility plus completely irregular periods

On examination of these patients fixity of uterus or tenderness could be detected in 6 cases only.

The following conditions were found at operation:

	Cases		Cases
Multiple myomata	12	Tuberculous salpingitis	1
Single myoma	12	(R. salpingectomy; left tube patent)	
Endometriosis of both ovaries	3	Ovary adherent to pelvic floor	1
Early endometriosis of one ovary ..	2	Chronic salpingitis plus pelvic appendix ..	1
Follicular cystic disease of ovaries ..	12	Chronic salpingitis nodosa with patent tubes	1
Large endometrial cyst of ovary ..	2	Right hæmatosalpinx; left tube patent ..	1

GROUP IV FOLLOW-UP

1 patient who had endometrial cyst removed in 1946 had 1 child in 1950
1 patient with early endometriosis in 1949 had 1 child in 1953 and a miscarriage in 1952
1 patient with cystic ovaries operated upon in 1946 had an ectopic pregnancy in 1947
1 patient separated from husband one year after operation
5 husbands known to be subfertile
1 patient had an operation for intestinal adhesions nine months after operation

Pathology.—16 simple myomata. 6 had hyaline degeneration (in 7 cases no report on myomata). In 7 patients section of pieces of ovary showed endometriosis as confirmed by pathological examination.

OVERALL RESULTS in Group IV: 24 cases of myomectomy associated with operations on tubes and ovaries; 2 full-time children.

OPERATIVE TECHNIQUE

The technique of the operation is of course well known. The much more complete relaxation obtained by *d*-tubocurarine chloride makes it easier to control the uterus. "The good uterine contraction is due to the light anæsthesia which can be used after the injection of the relaxant, rather than to any inherent pharmacological action of the drug itself" (Evans, 1954). In other words gas and oxygen alone is sufficient, no ether being used. I feel sure that this type of anæsthesia is one of the reasons why much less bleeding now occurs during these operations.

A fair-sized incision in the uterus is made over the most prominent myoma, cutting straight down on the myoma through the capsule taking care to avoid the cornua and large vessels. Before making this incision in the uterus 0·5 mg. ergometrine or less is injected in a series of small injections on the line where it is intended to make the incision into the uterus. Then having cut through the capsule by a fair-sized incision, I loosen the myoma from its capsule using the handle of the knife and fingers, doing practically no cutting. Then two or more Littlewood's tenaculum forceps are used to grasp the myoma and it is twisted round and round. This often twists off the small myomata.

In larger tumours artery clips are put on the remains of the capsule and the myoma removed. All bleeding points are caught by artery forceps. These tags and strands are tied off with stitches of twenty-day catgut and a few mattress sutures of catgut placed in the

uterine wall from side to side to obliterate the cavity from which the myoma has been removed. It is a mistake to tie these sutures too tightly as this may cause necrosis of the uterine muscle. The redundant part of the uterine wall superficial to the cavity on each side is folded over and the raw edges inverted by deep Lembert sutures of plain catgut.

It is very unusual to have to cut away any of the uterine substance except in very large myomata. The wound in the uterus is then covered with a piece of living omentum which is fixed with a few stitches of fine plain catgut. This is partly to prevent adhesions of bowel to the site and partly to prevent epithelial elements from working their way outwards, especially if the cavity of the uterus has been opened.

In one or two cases where hysterectomy has been necessary some years after myomectomy I have found the omentum still firmly fixed on the surface of the uterus.

In my opinion if this technique is adopted there is no need to use any form of clamp or tourniquet on the cervix. Personally I have not used one for a long time. In the very large tumours I do occasionally grasp the cervix for a short time or ask my assistant to do so.

In multiple myomata, if convenient, we follow Victor Bonney's technique of removing as many tumours as possible through one incision, but personally I have come to the conclusion that the number of incisions made in the uterus does not matter much provided they are securely sewn up.

If the cavity of the uterus is opened, it is advisable to sew up the uterine muscle with care close to where the opening has been made into the cavity.

One should be on the look-out for rise of temperature in these cases post-operatively and be prepared to treat it at once. If the cavity is suspected of being septic we usually give 1 million units of penicillin at once and carry on as required.

It is most important to handle the uterus gently and to avoid unnecessary trauma in every way. For this reason I prefer, if necessary, several clean cuts into the uterus to doing elaborate tunnelling manœuvres.

Any post-operative bleeding *per vaginam* can be dealt with by injection of ergometrine. I have had no dangerous degree of post-operative bleeding so far.

In my opinion it is very important that patients who have had myomectomy done should resume married life as soon as they feel well and are able to do so. No instructions should be given to wait for any given period of time. In many cases they have already waited for years to have a child, and it is advisable that they should be encouraged to start a child as soon as possible. It is psychologically good and takes away fear. Fear of complications in childbirth may often cause patients to avoid pregnancy unless they are reassured after the operation.

As noted earlier, Sir Arthur Gemmell (1936) concluded that approximately one-quarter of the patients submitted to conservative operation for fibroids later conceived—a result he considered well worth striving for. In presenting this personal series of cases, though the figures may not be statistically significant, nevertheless, I hope I have shown that with careful selection of cases, it is possible to obtain successful results. It is my firm opinion that myomectomy performed primarily for the cure of infertility should be undertaken more frequently.

I wish to acknowledge my indebtedness to my colleagues at the Royal Free Hospital for permission to use their records and to Dr. Isobel Beswick for reviewing the pathological findings.

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Mr. H. G. E. Arthure reported on a series of 45 cases of abdominal myomectomy performed at Charing Cross or Mount Vernon Hospital since the war. Only 17 of these patients had been pregnant before the operation, but the others were not necessarily infertile, and 13 were unmarried. 33 married women having a hysterectomy for fibroids were found to have produced 58 children between them, which is little below the national average.

In only about 10% of myomectomies does the patient complain of infertility, and there is little evidence that fibroids cause infertility apart from the pedunculated submucous fibroid. Myomectomy will not affect other associated causes of infertility, and it is unlikely to cure compression of a fallopian tube by a fibroid, if this has occurred. It seems improbable, therefore, that myomectomy will improve the chances of conception, and the percentage of women trying to conceive and becoming pregnant after myomectomy (25–30%) might be the same or even higher if no operation had been performed.

There is little doubt that fibroids may be a factor in causing a miscarriage or premature stillbirth, and if so myomectomy is, of course, justified. These patients have proved their fertility, and are likely to conceive again.

The speaker questioned the use of myomectomy clamps, firstly because of the risk of bleeding from the bed of a fibroid when the clamps are removed, and secondly because of the possibility of causing thrombosis from trauma.

Mr. D. B. Fraser said that the records of 100 abdominal myomectomies performed at St. Bartholomew's Hospital between the years 1947 and 1954 had been studied: only 12 of these fall into the group under discussion as defined by the President, with infertility the *only* presenting symptom. Of these—whose average age was 36—only two were known to have had successful pregnancies subsequently.

22 more cases in the group, who later had 8 successes, presented with infertility as ordinarily defined, as part of their symptom complex. The average age of the whole group was 33½; 23 were single women and with the remaining 43, presented with menorrhagia, a lump or pressure symptoms with discomfort. The material was too small to draw any conclusions in relation to improvement of fertility by myomectomy.

No major complications occurred in this series and the operation did not appear to be more dangerous than hysterectomy.

On the point of technique, the use of a rubber catheter encircling the lower part of the uterus seemed to be the simplest method of controlling hæmorrhage while operating.

Other speakers in the subsequent discussion stressed that Miss Dearnley had been exceptionally fortunate in her results and that many other operators had not had such a high percentage of subsequent pregnancies. It was generally agreed that it paid to exercise care and skill in the choice of patients for any particular line of research.

Section of Epidemiology and Preventive Medicine

President—MAURICE MITMAN, M.D., F.R.C.P., D.P.H.

[*September* 15, 1955]

Studies of Respiratory and Other Illnesses in Cleveland (Ohio) Families [*Summary*][1]

By JOHN H. DINGLE, M.D.

Elisabeth Severance Prentiss Professor of Preventive Medicine, School of Medicine, Western Reserve University, Cleveland, Ohio

A STUDY of illness in a selected group of normal families has been carried on for the past eight years by the staff of the Department of Preventive Medicine, School of Medicine, Western Reserve University[2] (*see* references). Because of the lack of accurate information regarding the occurrence and behaviour of illnesses—especially minor illnesses—in civilian populations, answers were first sought for rather obvious questions, such as: How much illness actually occurs? What are the types of illness? What is the cause of the illnesses? What is the important population unit in the spread of illness? Additional studies of the spread of illness and of specific diseases have also been undertaken.

The population of families is a highly selected one. After referral by private physicians and interviews with our staff, the families are chosen on the basis of probable stability in the community and intelligent co-operation. Economically, the families are in the middle and upper classes. The parents are young adults, all families have one or more children, and children constitute more than one-half of the population. On admission to the study, each member of the family receives a complete medical work-up which is repeated at annual intervals. Daily records of symptoms are kept by the mother for each member of the family and are reviewed weekly in the home by a nurse-field worker. At the time of illness a physician from the Department visits the patient, characterizes the illness clinically, records the epidemiological relationships and, in so far as possible, determines the ætiology or obtains appropriate specimens for that purpose.

In analysing the data, broad diagnostic categories are employed first, followed by more detailed analyses of each category. Leads to possible new entities are sought on the basis of the clinical, epidemiological or laboratory data.

Some of the results of the investigation suggest the following conclusions:

On the average, ten illnesses occurred per person per year, the highest attack rates occurring in children. Respiratory infections accounted for about two-thirds of the illnesses and comprised the largest category. Gastrointestinal illnesses were second most frequent, accounting for about 16% of all illnesses. Only 3% of the respiratory illnesses and about 2% of all illnesses could be treated effectively by antibiotic or sulphonamide drugs. Between September and April about 15% of the population acquired a new respiratory illness, usually the common cold, each week. School children introduced more colds into the home than any other family member, and pre-school siblings had the highest secondary attack rate.

In childhood males had more colds than females, but the reverse was true after puberty. More colds and other minor respiratory infections were acquired in the home than any other place in the community.

Tonsillectomy did not reduce the frequency or severity of common respiratory diseases, including the common cold and other viral infections of the respiratory tract.

The new respiratory tract viruses (variously termed the AD, RI, ARD, or APC group of viruses) have thus far been responsible for only a very small proportion of respiratory infections in this civilian population. A small outbreak of acute pharyngitis in children due to the type-3 virus has been described. No evidence has been found of infection in the children of this population with the type-4 virus which has been ætiologically associated with acute respiratory disease (ARD) in military recruits.

[1]The investigations forming the basis of this presentation were conducted under the auspices of the Commission on Acute Respiratory Diseases, Armed Forces Epidemiological Board, and were supported in part by the Office of The Surgeon-General, Department of the Army, and by grants from the Brush Foundation, the Robert Hamilton Bishop, Jr., Endowment Fund, Mr. Philip R. Mather and the Republic Steel Corporation.

[2]Collaborators in this study have included Drs. G. F. Badger, C. Curtiss, A. E. Feller, H. S. Ginsberg, E. Gold, R. G. Hodges, W. E. S. James, W. S. Jordan, Jr., S. Katz, R. Oseasohn, C. H. Rammelkamp, Jr., H. B. Rosenbaum, and I. G. Tillotson.

Two forms of gastro-enteritis have been defined, both apparently due to viruses. Confirmation has been obtained by experimental studies in volunteers.

It is hoped that the results of this study will help in the final goal of a better understanding of illness and of health, and in the development of better methods of diagnosing, treating, and preventing illnessess, especially the troublesome minor illnesses.

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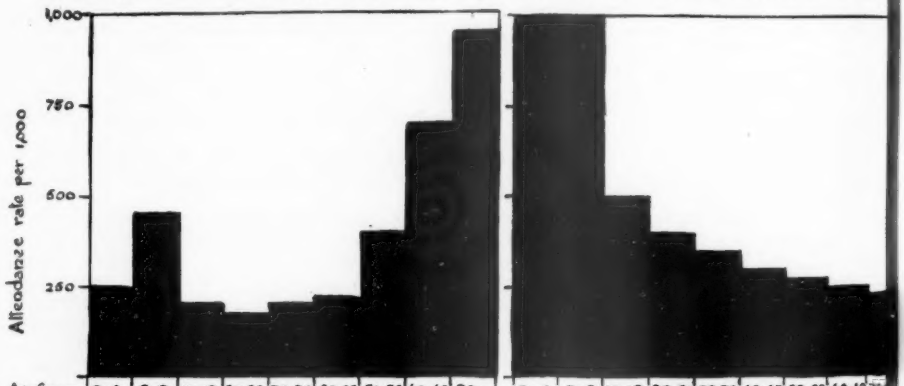
Dr. John Fry (Beckenham, Kent): Professor Dingle's paper will earn the gratitude of the general practitioners who have to deal with the huge mass of respiratory tract infections, on which so little work has, so far, been carried out.

The importance of the respiratory tract as a cause of morbidity is evident from the fact that at least 25% of all attendances in general practice are for some affection of this system. The general practitioner should therefore be in a favourable position to elucidate some of the many problems of respiratory tract infections both in the family and in the population as a whole. He is also in an enviable position in this country, for since the inception of the National Health Service he has the



Attendance rate per 1,000 at risk	0-4	5-9	10-19	20-29	30-39	40-49	50-59	60-69	70 +
	250	450	200	175	200	220	400	700	950

FIG. 1.—Incidence of respiratory tract affections at different ages.

	0-4	5-9	10-19	20-29	30-39	40-49	50-59	60-69	70
	1,000	1,000	500	400	350	300	275	250	225

FIG. 2.—Incidence of upper respiratory tract infections at different ages.

means by way of records, for investigation and follow-up in his practice, which is in fact an unselected community. He is able to study individuals, families, specific clinical entities, the more vague clinical syndromes of as yet unproven ætiology and he is also able to observe changes in distribution in the sexes and in the different age groups of the population.

For the past five years I have been keeping records in my own practice of some 5,000 patients in S.E. London and I would like to refer very briefly to some of the observations on respiratory tract infections.

For the sake of convenience it is easiest to divide the conditions into upper and lower tract infections. The former account for 15% of all attendances and the latter for 10%. Sex distribution is equal in the upper tract infections but there is a marked preponderance of males in infections of the lungs and bronchi. There is a fascinating difference in the age distribution of the two groups as seen in Figs. 1 and 2. It is evident, as Professor Dingle has pointed out, that it is the pre-school and early school child who is most liable to upper respiratory infections and this I can confirm. I would

like to stress that the natural tendency is for the conditions to remit around the age of 7–9 years, and we should bear this in mind when considering radical therapy such as tonsillectomy. Infections of the lungs and bronchi have quite a different age distribution, rising with age, this being accounted for by the appearance of chronic bronchitis which is so frequent in this country; in my own practice the incidence is around 30 per 1,000.

I find that there is a characteristic rise in the incidence of upper respiratory tract infections every year at the same time, the 39th and 40th weeks, and this is quite unrelated to the prevailing climatic conditions, but it is related to the start of the winter term at schools.

[*January* 20, 1956]

The Epidemiology of Chronic Disease in South Wales

By A. L. COCHRANE, M.B., B.Ch., D.P.H., and W. E. MIALL, M.B., B.S.

SUPERFICIALLY it may seem odd that the Pneumoconiosis Research Unit devotes some of its time to the study of the prevalence of common diseases in two communities, but its evolution has really been very logical. It can be conveniently summarized in three steps:

(i) The realization that if you are studying pulmonary disability you must study all common pulmonary and cardiac diseases.

(ii) The realization that populations of working miners are selected populations, and that the only unselected population of miners and ex-miners is a complete mining community.

(iii) The realization, after studying the mining community in considerable detail, of the need of a standard with which to compare our results. As Sir Henry Dale said "So much of scientific medicine is comparative measurement". We therefore chose an agricultural area in the hope that the prevalence measurements made there would act as norms.

The two communities we are studying are those of the Rhondda Fach and the Vale of Glamorgan. The former is the smaller area (1) on the map (Fig. 1). It is a somewhat isolated

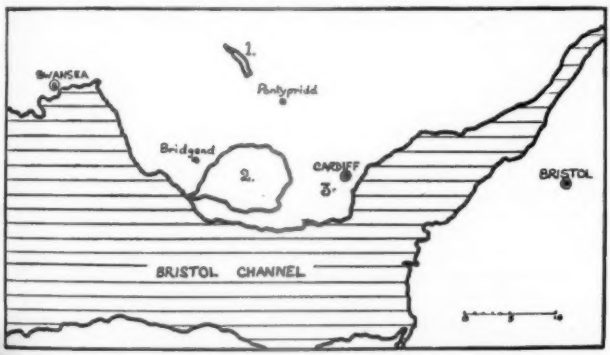


FIG. 1.—1, Rhondda Fach. 2, Vale of Glamorgan. 3, Pneumoconiosis Research Unit.

valley with a population of about 25,000 and a high population density. The other (2) is a relatively unspoilt agricultural area surrounding the small market town of Cowbridge. The total population is about 6,000. It has a very low population density.

The idea of doing this work has been "sold" to the two communities on the basis that we would attempt to eliminate pulmonary tuberculosis from the area if they would in return help us to do research on other diseases which might be preventable in the future. This approach appears to have worked well as we have had excellent co-operation. The refusal rate in our numerous surveys has only rarely been above 10% and has often been as low as 2%.

The work on the scientific side has also been co-operative. Most of the surveys have been carried out by the epidemiological and radiological teams, but we have had great support from our own colleagues at the Pneumoconiosis Research Unit, consultants in Cardiff, and Professor G. W. Pickering, Professor J. H. Kellgren, and Dr. W. R. Trotter.

Our objective is quite simply prevention, and as a first step in this direction we attempt to measure certain epidemiological indices. The measurement we most commonly make is that of prevalence.

The measurement of prevalence is to some extent an end in itself. Prevalence measures better than any other index the actual load on the community caused by the disease. From the point of view of prevention it can furnish clues as to ætiology in two ways: (i) by establishing differences in prevalence of the same disease in different areas, or between different occupational groups in the same area; (ii) by providing a complete unselected

population of a particular disease group whose characteristics can then be compared with a proper control group—and by "proper" control group we mean a group, free of the disease in question, of the same age and sex constitution as the group with the disease, chosen by some random process from the same population as that of the diseased group. We do think that this approach to the planning of comparisons between diseased groups and controls is preferable to the more usual comparison between a selection of a particular disease group, attending a particular hospital at a particular time, and a volunteer group from the skin out-patients.

Prevalence measurements also serve as a baseline for forward-looking studies in which the rate of appearance (attack rate) of new cases is studied. Such studies take a long time and we have so far only completed measurements of the attack rate of tuberculosis and progressive massive fibrosis.

The technique we use varies a little for each disease, but in general we apply some screening test to the whole population or to the sample of it which we are investigating, and then apply more detailed tests to the section of the population picked up by the screening tests. For instance, a P.A. chest X-ray is the screening test for tuberculosis and bronchial carcinoma, a post-prandial urine test for diabetes, and a questionnaire for asthma. Standardized clinical tests are applied to those picked up by the screening tests. Some tests are completed in the home, some in mobile vans, some in local halls, and for some tests the people are motored to hospital.

We cannot, of course, study all diseases. We are limited in several ways. We only have one small team and can therefore only study small communities. We can therefore only study common diseases, i.e. those with an average prevalence greater than 1 per 1,000. We hope, for instance, to study the epidemiology of bronchiectasis, but consider disseminated sclerosis too rare. We do not altogether regret this limitation to common diseases. The medical profession pays far too much attention to rare as opposed to common diseases, in the same way as it is preoccupied with treatment at the cost of prevention.

We are also limited in another way. We do not consider it worth while making measurements for which it will be impossible to make comparable measurements in other areas. The critical point here is the reproducibility of the lowest level of diagnosis. This concept has led us into many studies of medical observer error, which start by amusing and end by depressing us. Practically, we believe that the diagnosis of mental disease is subject to too great an observer error to make prevalence measurements justifiable at present, and difficulties in reducing the observer error in the diagnosis of bronchitis have slowed down our work on this considerably.

A third but rarer group of limitations are ethical considerations. It sometimes happens that one is tempted to apply some definitely unpleasant test to large numbers of people who would be most unlikely to benefit from the test or its results. A case in point is the bronchogram. It would be very interesting to know the results of doing bronchograms on a random sample of people with normal chest X-rays, but we consider it would be incorrect to do this.

Table I shows the list of diseases and conditions which are being studied in the two communities.

TABLE I.—MEDICAL CONDITIONS EXAMINED QUANTITATIVELY IN THE RHONDDA FACH AND THE VALE OF GLAMORGAN

Distribution	Blood pressure	
	Pulmonary disability	
Prevalence	Pneumoconiosis	Diabetes
	Tuberculosis	Rheumatoid arthritis
	Bronchiectasis	Goitre
	Bronchitis	Asthma
	Bronchial carcinoma	Coronary disease
Attack rate	Tuberculosis	
	Progressive massive fibrosis	

[A series of slides were then shown, illustrating some of the results and some of the technical points that have emerged, such as: (1) The differences in prevalence of diabetes, asthma and tuberculosis in the two communities. (2) The comparison between "known" and "unknown" cases in tuberculosis and diabetes. (3) The epidemiology of the Caplan syndrome. (4) The shapes of various age-sex specific prevalence curves, and the possible explanations of the differences. (5) The different results obtained when attempting to correlate X-ray category of pneumoconiosis with pulmonary disability according to the type of population that was investigated.]

We do not claim that this "community" approach is the only one to the epidemiology of the chronic diseases. Some things can possibly still be learned by juggling with death-rates and comparing hospital patients with some type of out-patients, but we believe that much more can be learned from community studies.

Section of General Practice

President—GEOFFREY BARBER, O.B.E., M.A., M.B.

[*December* 21, 1955]

DISCUSSION ON STAPHYLOCOCCAL INFECTION

Dr. Leonard Roodyn (General Practitioner, Woodberry Down Health Centre, London):

Staphylococcal Infections in General Practice

As general practitioners, we encounter staphylococcal infections almost daily in our patients. Boils, styes, conjunctivitis, whitlows, wound infections and infected eczema form a large proportion of the septic lesions which we are called upon to treat. With the provision of full bacteriological facilities by the Public Health Laboratory Service, the family doctor has now become well placed to study some of the problems presented by these infections.

Age incidence.—Table I shows the age distribution of 81 patients with staphylococcal

TABLE I.—AGE DISTRIBUTION OF 81 PATIENTS WITH STAPHYLOCOCCAL INFECTIONS

	Under 5	5–19	20–44	45–64	Over 65
Random sample from practice	15%	28·6%	37·8%	10·8%	7·8%
Patients with staphylococcal infection..	1 (1·3%)	33 (40·7%)	41 (50·6%)	3 (3·7%)	3 (3·7%)

From: Roodyn, L. (1954) By kind permission.

infections. About 90% of cases occurred during adolescence and early adult life; indeed the incidence in this age group is so high, that when Dr. W. P. D. Logan of the General Register Office investigated the diseases causing most consultations among young adult males he obtained the results shown in Table II. Boils were only slightly less common than acute influenza in young adult males.

TABLE II.—DISEASES CAUSING MOST CONSULTATIONS IN MALES AGED 15–44

Bronchitis	Cold	Influenza	Boils	Gastritis
950	837	711	674	484

From: Logan, W. P. D. (1954) By kind permission.

Sites of lesions.—Fig. 1 demonstrates the high incidence of lesions occurring in relationship to the nose: nose (8%), eyelids (22%) and area of face around the nose (14%); also the importance of chronic irritation and trauma of the skin; extensor surface of the forearms (19%), back of neck (5%) and the point of the shoulder (3%) in females often associated with a tight brassiere strap.

Bacteriophage-typing of Staphylococci

In the further study of staphylococcal infections, the phage method of typing proved of the greatest value. A total of 181 strains of staphylococci were tested and 147 (81%) of the cultures were typable. Of the 113 strains isolated from the frank pus of boils and styes, 96 (85%) were typable. The 68 nasal strains yielded a lower proportion of typable strains: 51 (75%). In the majority of staphylococcal infections, the phage method of typing could be applied with success.

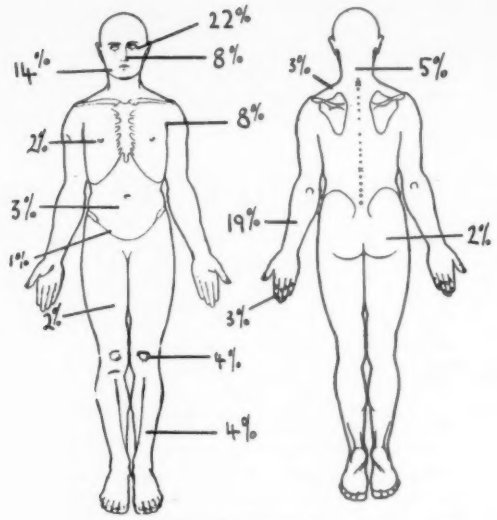


FIG. 1.—Site of lesions in 81 patients.

Williams and Rippon (1952) have described three broad groups (I, II, and III) of phage patterns, and according to Rountree (1953) working in Sydney there is a preponderance of Group II strains in cases of boils.

This was confirmed in the investigation on Woodberry Down Estate where it was found that of 70 penicillin-sensitive strains of staphylococci obtained from the pus of boils, 32 (46%) belonged to Group II.

Employing this useful method, I shall discuss three important features of staphylococcal infection. Firstly recurrent staphylococcal infection, secondly drug-resistant strains and, finally, the epidemiology of staphylococcal infections.

Recurrent staphylococcal infection.—Boils and styes show a marked tendency to recur and 13 patients in this series (or about 1 in 6) developed further lesions, usually within a few months of the first infection, but often as long as one or two years later and some patients seemed to have had episodes of staphylococcal infection throughout their lifetime.

There are two possible explanations of the nature of these recurrent infections.

These patients could be suffering from repeated fresh infections with different strains of staphylococci. For example, a man may have had a boil due to phage-type 3B to which he developed some immunity, only to succumb a few months later to an infection with phage 52A to which he was not immune.

Or alternatively, these recurring infections may be simply exacerbations of infection with the original phage-type.

Now in all of the 13 cases of recurrent infection studied in this investigation, the same phage-type of staphylococcus was recovered from the later lesions as from the first. Here is one example:

Miss M. F., aged 27 years.	9.8.51: Boil on lt. elbow	Phage 42E
	9.10.51: Boil on lt. knee	Phage 42E
	29.9.52: Boil on rt. axilla	Phage 42E

These patients have therefore failed to eliminate a particular strain of staphylococcus which, after a first infection, became established in their body.

But where was this unconquered staphylococcus hiding?

In the case of styes, it could be said with reasonable certainty that the source of infection lay in the nostrils. Of 22 cases of styes investigated 17 (or 77%) carried an identical strain of staphylococcus in the nose and eyelid. The staphylococcus often entered the nose in association with a virus infection of the upper respiratory tract. For example, in measles, styes developed in the convalescent stage and phage-typing showed that there was a

secondary infection of the anterior nares with *Staph. aureus* and then probably direct spread to the eyelids. A similar event occurred in the common cold and many practitioners must have heard patients say that they have one cold after another and that they are always breaking out in styes.

In the case of recurrent boils, however, the nasal staphylococci played a smaller role. Of the 13 patients with recurrent lesions, 7 of them did carry identical strains in nose and lesion, but 3 patients had recurrences in the absence of nasal staphylococci, as in the following case:

Mr. M. K., aged 30 years.	3.9.52:	Boil on lt. forearm	Phage 3C
		N/S	No staphylococci.
	31.7.52:	Boil on rt. forearm	Phage 3C
		N/S	No staphylococci.
	13.10.53:	Boil on lt. elbow	Phage 3C
		N/S	No staphylococci.

In 3 other cases of recurrent boils, there were nasal staphylococci but they were of a different phage-type from those recovered from the lesion.

A particularly illustrative case is:

C. B., aged 11 years.	29.12.51:	Rt. stye	3B	P.S.
		Lt. stye	3B	P.S.
		Boil on leg	52A	P.R.
		N/S	3B	P.S.
	14.11.52:	Boil on face	52A	P.R.
		N/S	3B	P.S.

The nasal strain (3B) was clearly associated with the styes (3B) but played no part in the production of the boil (52A). When there was a recurrence nearly a year later, it was the strain originally recovered from the boil (52A) which once again reappeared.

This suggests the importance of the chronic skin carriage of staphylococci in cases of recurrent boils—particularly in the deeper layers of the epidermis, the sebaceous glands, the sweat glands and the hair follicles. It is here that the staphyloccocci probably reside, perhaps for months or years on end, only to erupt into a boil if the skin is damaged or if the patient's resistance is lowered by overwork, worry or diabetes.

Further study is needed of the behaviour of the staphyloccoci in the skin itself in cases of recurrent boils.

Penicillin-resistant staphylococcal infections.—Of 93 strains of staphylococci obtained from the pus of boils and styes in general practice, 23 (25%) were persistent to penicillin. The strains obtained from the nasal carriers yielded a higher proportion of resistant organisms, 21 (30·9%) of 68 tested.

So that in general practice we are still in the favourable position of the hospital doctors of 1946 or 1947, when Dr. Barber, for example, found that the incidence of penicillin-resistant infections among in-patients for these two years was 14% and 38% respectively.

The different phage-types of staphylococci seem to vary in the ease with which they throw off penicillin-resistant mutants. Of 23 resistant strains recovered from the pus of boils and styes, 12 belonged to Group I and 8 were not phage typable. Only 1 penicillin-resistant strain belonged to Group II.

The emergence of resistance in association with penicillin treatment has always been regarded as a very rare event. Reinfection with a different resistant strain is not likely to be the explanation of these cases, as it has already been demonstrated that recurrences are due to exacerbation with the original strain. It is more likely that the original lesion, which was penicillin sensitive, begins to discharge and after a few days resistance develops in association with this phenomenon and not necessarily with the treatment with penicillin, as in this case:

Mr. W. R.	13.5.52:	Boil on groin	52A/79	P.S.
		N/S	70	P.S.

He was treated with crystalline penicillin 500,000 units daily for five days. The boil discharged for a few days and then healed. He developed a recurrence:

20.6.52:	Boil on shin	52A/79	P.R.
	N/S	Not typable	P.S.

The strain had now become penicillin resistant. Over three years later his wife developed a staphylococcal infection:

A. R. 23.11.55: Boil on nose 79 P.R.

It was interesting that the infection was caused by the same phage type as that recovered from the husband's boil and that the husband's nasal strain was not passed on to the wife. Cross-infection with a resistant strain occurred from the lesion and not from the nasal cavity.

Indeed it was difficult to determine the role that the nasal carriers of penicillin-resistant staphylococci played in the spread of resistant infections. Thus 3 patients are described who carried resistant nasal strains and yet developed penicillin-sensitive infections:

C. C.	33	Boil on neck	52A	P.S.
		N/S	—	P.R.
T. B.	14	Boil on abdomen	3C	P.S.
		N/S	42C	P.R.
F. H.	31	Boil on neck	71	P.S.
		N/S	—	P.R.

If these patients could not even infect themselves, it is a little difficult to visualise how they would be capable of spreading their penicillin-resistant nasal strains to other people.

Epidemiology of staphylococcal infections.—The phage-typing of staphylococci provides a useful method of studying the spread of these infections within the family unit.

The immediate infectivity of a boil or stye appeared to be quite low as only once did simultaneous lesions occur in another member of the household. But in about 1 in 4 of the cases of boils, if the other members of the family were followed up over a period of months, first one and then another developed staphylococcal infections.

This was observed in a total of ten families and a typical staphylococcal family is shown:

Case	Age		Date	Lesion	Phage
Y. S.	31	Mother	6.5.52	Boil on chin	52A
M. S.	13	Daughter	19.4.53	Boil on leg	52A/79
A. S.	39	Father	10.7.53	Boil on axilla	52A
G. S.	14	Son	24.11.55	Boil on neck	52A/79

In this respect the family units present in a miniature and easily studied form the same problems as the surgical wards and maternity units.

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Dr. Mary Barber (Department of Bacteriology, St. Thomas's Hospital Medical School, London):

Staphylococcal Infection in Hospital

In spite of the *ubiquity of the staphylococcus* and the *frequency of its attacks*, our ignorance of staphylococcal infection is abysmal. Many of us have become so familiar with the organism that we treat it with contempt, or perhaps affection, until it strikes us unexpectedly. Sir Alexander Ogston, who discovered and named the staphylococcus in 1880, went so far as to say that he had always regarded it as "*a friendly little chap*" until he got a staphylococcal lung abscess.

It is one of the most fascinating, as well as baffling, problems of clinical medicine that contact with what appears from laboratory tests to be a single strain of *Staph. pyogenes*, can, in different individuals, or even the same individual on different occasions, have such widely varying results as, for example, no reaction, simple nasal carriage, a small septic spot, a boil, a carbuncle, osteomyelitis, fatal pyæmia.

The story is familiar of a patient who squeezes a tiny staphylococcal spot on the face, perhaps in the neighbourhood of the angular vein, and develops thrombosis of the cerebral sinuses. I shall always remember one such case, a woman whose life was saved by penicillin

but only after she had lost one eye. Yet how many of us have squeezed a similar lesion on the face and got away with it?

Pathogenicity of microbe and resistance of host.—Like all forms of infection, that due to the staphylococcus depends on both the virulence of the microbe and the resistance of the host. A great deal of work has been done on the virulence of pathogenic staphylococci and they are known to produce a number of toxic agents. Of these, coagulase, fibrinolysin and hyaluronidase are probably concerned with tissue invasion, while α-toxin and leucocidin have a more direct toxic effect. Quantitative studies, however, attempting to grade the virulence of strains of *Staph. aureus* isolated from different sources, have so far proved somewhat inconclusive.

The resistance of different individuals to staphylococcal infection remains something of a mystery. Most adults in this country have developed antibodies to staphylococci and many of its toxic products, but this does not render them immune to staphylococcal infection. Recently, Dubos and his colleagues (1955) at The Rockefeller Institute, New York, have studied resistance to infection from a rather different angle. They have shown that a variety of procedures which disturb animal metabolism, notably starvation, increase the susceptibility of mice to infection with staphylococci and other bacteria. These important observations may help to explain the severity of many cases of post-operative infection with *Staph. aureus*.

Antibiotic-resistant infection.—The outstanding feature of staphylococcal infection in hospital to-day is the high incidence of cases due to antibiotic-resistant strains. Since most other bacteria have shown far less propensity to yield antibiotic-resistant variants, staphylococci are to-day the most important source of infection in most general hospitals.

Studies which include bacteriophage-typing of strains isolated have made it clear that the high incidence of antibiotic-resistant staphylococcal infection in hospitals is due to the fact that these institutions are becoming breeding grounds for a few antibiotic-resistant strains of *Staph. aureus*, which are selected by the widespread use of antibiotics (cf. Barber and Whitehead, 1949; Rountree and Thomson, 1949; and Barber and Burston, 1955). Most clinical cases appear to be the result of hospital cross-infection and a very high proportion of nurses in these institutions carry similar strains in the anterior nares. In the community at large, most cases of staphylococcal infection are still sensitive to antibiotics, but Rees *et al.* (1955) report that penicillin-resistant staphylococcal infection is becoming quite common amongst out-patients.

Maternity units.—Newborn babies, being born free from bacteria, are particularly prone to colonization with antibiotic-resistant strains of *Staph. aureus*, and more than half the babies born in hospital go home carrying such strains in the anterior nares. This has been shown to occur not only in a department where staphylococcal infection of the newborn was a problem (cf. Barber, Hayhoe and Whitehead, 1949) but also in a unit free from sepsis (Barber *et al.*, 1953). In both departments the strains appeared to be passing from the nurses to the babies, and why in one department this happened without an outbreak of sepsis remains doubtful. It seems probable that strains carried in the nasopharynx are less virulent than those isolated from infective processes, although this is difficult to demonstrate in the laboratory.

Post-operative infection.—In a recent survey in a general hospital (Barber and Burston, 1955), it was found that 24 of 100 staphylococcal infections occurring over a six-month period were due to strains resistant to penicillin, streptomycin and all three tetracycline antibiotics. Of these 24 cases 17 followed surgical operation, and the remaining 7 consisted of various types of chronic or recurrent infection in patients who had been under hospital treatment for many months.

The 17 strains isolated from post-operative infections all belonged to phage-group III and 12 were of the same phage-type. Nevertheless, it was impossible to trace them to a single source of infection. The patients were in 10 different wards and had been operated on by nine different surgeons in three different operating theatres. Few nurses in the wards involved carried strains with this antibiotic-sensitivity pattern. There was, however, in many instances a close association between a post-operative case and one of the patients with a chronic infection due to a similar strain. Since the latter patients either had superficial lesions or pulmonary infections with staphylococci in the sputum, it seemed probable that they were the main reservoir of infection, whatever the actual route of spread.

Prevention.—The control of hospital cross-infection is not a simple one. It seems certain that clean and septic cases should be operated on in separate theatres and nursed in separate

wards. It is probable that most hospitals ought to be reconstructed with much smaller wards.

Antibiotics should only be used for the treatment of infections likely to respond to them and then in full doses for adequate periods. Their use prophylactically should be strictly limited and they should not be used as a cover for negligent aseptic technique. As new antibiotics are discovered, it would be well to keep one or more in reserve, or if all members of a hospital staff could be prevailed on to co-operate, a system of rotation might be worked out whereby the antibiotics in use in a hospital were changed every six months.

The general practitioner may well conclude that the moral of all this is that he should keep his patients out of hospital. He should, however, take warning and see that the same situation does not occur among the community at large. This depends on the care with which antibiotics are used to-day. In particular, the broad-spectrum antibiotics should be regarded as dangerous drugs. At the risk of an outcry from busy general practitioners, I give it as my opinion that it is a pity such antibiotics can be administered orally. It makes it a little too easy to prescribe them for an undiagnosed pyrexia.

Louis Pasteur posed the question: "La vie sans microbes est-il possible?" Nowadays our point of view has changed and we are concerned not to be free from bacteria, but to live with the right ones. In using the broad-spectrum antibiotics, let us never forget that they destroy the normal bacterial flora of the body, thus leaving the house empty for "seven other devils" to enter in.

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Section of Radiology

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[*November* 18, 1955]

Some Rare Causes of Vomiting in Infancy and Childhood

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THE role of radiology in the investigation of the vomiting child is limited in its scope, those cases presenting positive radiological signs being grouped as a rule into well-recognized and familiar patterns.

I wish to draw attention in this paper to several cases where radiology not only demonstrated the cause of the vomiting but also revealed the presence of an unusual and rare condition as the ætiological factor.

ILLUSTRATIVE CASES

Case 1.—Male, aged 9 months.

First seen in the out-patient department, with a history of vomiting immediately after solid foods but able to retain fluids without difficulty. He had a stridor but physical examination was negative, the infant healthy and thriving and a totally unexpected finding in the routine X-ray of chest was the presence of a sixpenny piece in the upper mediastinum at the level of the second dorsal vertebra (Figs. 1 and 2).

As it is uncommon for a sixpence to lodge at this level at that age, a barium swallow was given and revealed the presence of a pouch or diverticulum about 2 cm. in diameter, arising from the œsophagus and situated posteriorly and to the right of the œsophagus just below the level of the impacted coin, with resultant narrowing of the œsophageal lumen. This decrease in the calibre of the œsophagus was sufficient to prevent the descent of the foreign body. The sixpence was then removed without difficulty from the upper end of œsophagus (Fig. 3).

FIG. 1.—A.P. view showing sixpence and pouch.

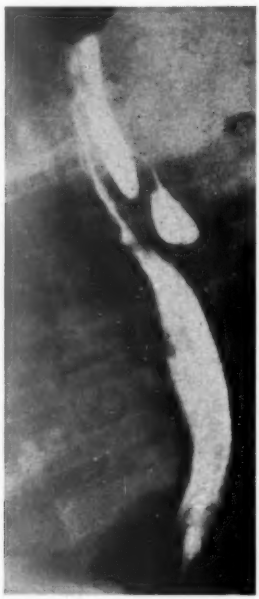

FIG. 2.—Lateral view of pouch and coin.

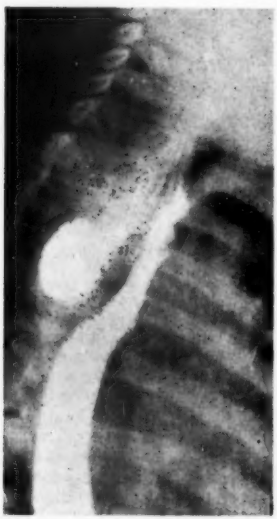

FIG. 3.—Pouch after removal of sixpence.

Further investigation of the pouch showed it to possess a narrow neck which was freely distensible and careful screening showed the pouch to be contractile and capable of emptying its contents into the œsophagus by muscular contraction of its walls. The mucosal folds of œsophagus were noted to be continuous with that of the pouch and there was little doubt that the pouch consisted largely of muscle fibres.

At first sight, the appearances resemble the pharyngeal pouch or pulsion diverticulum seen in elderly patients due to a protrusion of mucosa below the crico-pharyngeus muscle. These diverticula can project into the upper mediastinum but diagnosis of pharyngeal pouch cannot be sustained in view of the following facts:

(1) This diverticulum originates below the upper end of œsophagus.

(2) The walls of the pouch in this case are contractile and the possession of a muscular coat cannot be correlated with a pulsion diverticulum which consists solely of protrusion of mucosa.

(3) The age of patient. Pharyngeal pouches are almost unknown in infancy.

Duplication of œsophagus must also be considered in the differential diagnosis but the site and the fact that it communicates with the œsophagus renders this diagnosis unlikely.

My personal view is that this represents a variation of œsophageal atresia, hitherto undescribed. There is a rare variety of œsophageal atresia where the blind upper pouch is connected with the lower œsophageal segment by a fibrous cord. If this cord had developed further to become patent and canalized, then it could well be depicted as producing the appearance seen in this case.

Some months later this child was readmitted because of regurgitation of food following a meal of carrot purée. Barium swallow showed the pouch to be filled with non-opaque food residue preventing the entry of barium.

Œsophagoscopy revealed the pouch filled with carrot. The carrot was removed, and he was able to swallow without difficulty. This boy is now aged 2½ years and a recent barium swallow showed an appearance identical with those observed at previous examinations. He now eats a solid, varied diet without difficulty. He is symptom free, and above normal weight for his age.

Case II.—Female, aged 18 months.

She was admitted to a medical ward, grossly underweight with a history of persistent vomiting. Infection was excluded, and a barium meal revealed the presence of a distended stomach with duodenal ileus (Fig. 4).

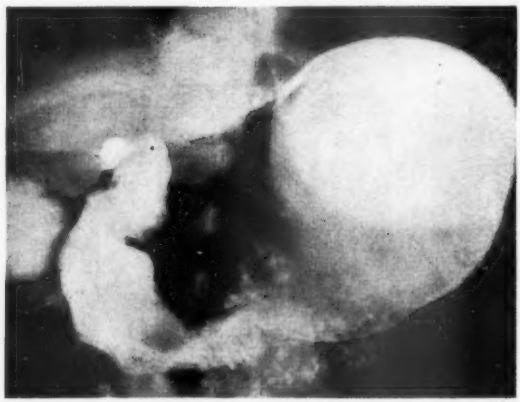

FIG. 4.—Dilated duodenal loop behind antrum of stomach.

In view of the evidence of duodenal obstruction, a laparotomy was performed and a duplication of bowel or enterogenous cyst, 7·5 cm. by 3·75 cm., was seen at the duodeno-jejunal flexure narrowing and compressing the adjacent lumen of duodenum. Resection presented difficulty and a retro-colic duodeno-jejunostomy was performed with good result. This is the third case described in the literature of enterogenous cyst producing an obstruction in the terminal part of the duodenum. The two previous cases reported in the literature occurred in adults.

Case III.—Female child, 8 years old, with a chequered history of intermittent bouts of vomiting. When 10 days old, she began to vomit after her feeds, the vomitus being greenish-brown and occurring a considerable time after meals. She continued to vomit at intervals of approximately one week but as she grew older the vomiting bouts became less frequent. Investigation in various hospitals failed to reveal any specific cause to account for the vomiting and she was treated on empiric grounds. For two months prior to her last admission, vomiting increased in frequency and she also complained of abdominal pain relieved by vomiting. She was 60% of her expected weight and abdominal examination revealed no abnormality.

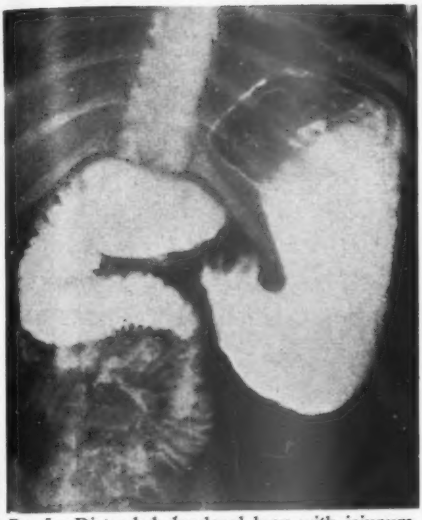

FIG. 5.—Distended duodenal loop with jejunum displaced to right.

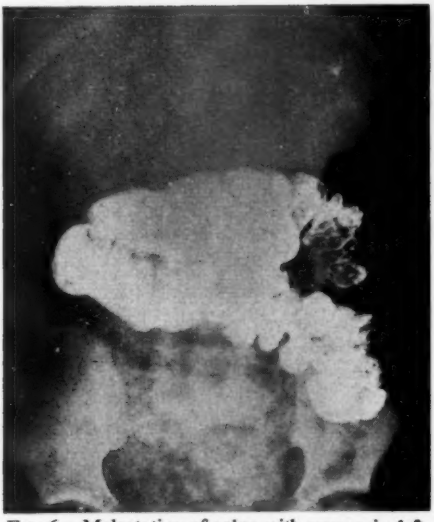

FIG. 6.—Malrotation of colon with cæcum in left iliac fossa.

A barium meal (Fig. 5) showed a normal œsophagus with slight enlargement of the stomach and distension of the whole of the duodenal loop which showed reverse peristalsis and narrowing of the third part of the duodenum which was less sharply angulated than is customary at the normal duodeno-jejunal flexure. No intrinsic lesion was identified in the duodenum and the duodenal ileus was attributed to external pressure on the third part of the duodenum. The obstruction was partial and after a short interval the barium passed freely into the jejunal loops which were somewhat collapsed and situated abnormally on the right side of abdomen, the ileum being displaced to the left. A follow-through showed a malrotation of the colon, the cæcum overlying the left iliac blade (Fig. 6).

Conclusion.—Malrotation of colon with intermittent volvulus of mid-gut and compression of duodenum by torsion at the mesenteric root. These findings were confirmed at operation. The volvulus was undone and a peritoneal band crossing the junction of the second and third parts of the duodenum was divided, freeing the obstructive duodenum. A post-operative barium meal showed a straight duodenum and there was no evidence of duodenal stasis. A four-hour film demonstrated the terminal ileum and cæcum in their normal situation and a barium enema confirmed the correct replacement of the colon.

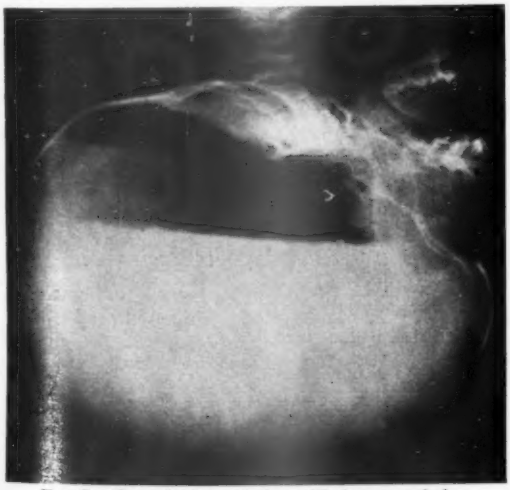

FIG. 7.—Gross hydrocephalus. Hydranencephaly.

Case IV.—That vomiting may be due to factors outside the gastro-intestinal tract must be borne in mind, as in this case, of an infant with a history of vomiting and increasing enlargement of her head. Before a diagnosis of hydrocephalus was established, the possibility of chronic subdural hæmatoma had to be excluded. A ventricular tap was done, C.S.F. was removed and air introduced (Fig. 7). The films showed a gross hydrocephalus of unusual type.

Post-mortem findings.—The cortex of brain formed a thin membrane no thicker than normal peritoneum with only the basal ganglia and cerebellum recognisable at the base of the skull. The

cause of the gross hydrocephalus was a congenital atresia of the aqueduct of Sylvius and the condition was almost identical with that described in hydranencephaly.

Case V.—A newborn female infant who regurgitated all her feeds through her mouth and nose immediately after feeding. A lipiodol swallow (Fig. 8) showed a hold-up of lipiodol in the pharynx and hypopharynx with spill-over of opaque medium into the trachea and nasal pharynx.

A rubber catheter was passed without difficulty into œsophagus and no intrinsic abnormality was noted in the œsophagus when outlined by lipiodol (Fig. 9).

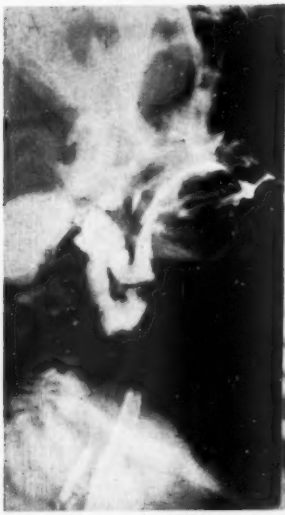

FIG. 8.—Obstruction of pharyngo-œsophageal junction.

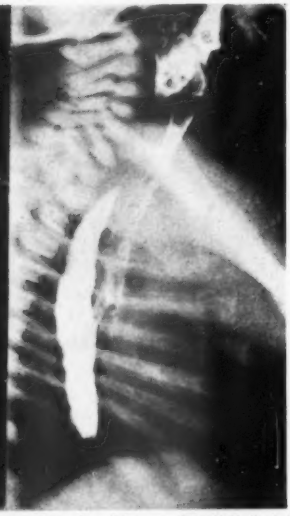

FIG. 9.—Note spill of lipiodol into trachea. Rubber catheter in œsophagus.

The appearances favoured a diagnosis of neuromuscular dysfunction at the pharyngo-œsophageal junction with regurgitation through nose and into trachea. The cause of this inco-ordination was not apparent but in view of the prevalence of poliomyelitis at that particular period, bulbar palsy had to be considered. A gastrostomy was performed as a life-saving measure but the feeds were regurgitated from the stomach into the œsophagus and thence into the trachea, the baby dying shortly afterwards from aspiration pneumonia.

Post-mortem.—Detailed histological studies failed to reveal any abnormality of any nature in the pharynx, œsophagus or nervous system and there was no evidence of poliomyelitis.

The exact nature of the lesion resulting in the inability to swallow in this case remains obscure although the lipiodol swallow demonstrated a form of achalasia at the pharyngo-œsophageal junction. A possible factor is birth injury but this is hypothetical.

SUMMARY

(1) 5 cases, presenting with symptoms of vomiting or regurgitation of food, were investigated by routine radiological methods.

(2) In each case, X-ray investigation proved to be the basic method of establishing a diagnosis.

(3) Malrotation of colon with volvulus of mid-gut (Case III) occurring in older children, as in this case, should always be considered in the differential diagnosis of "cyclical" vomiting, especially if the history commences shortly after birth.

(4) The remaining cases are rare and unusual congenital anomalies.

ACKNOWLEDGMENTS

I wish to thank Professor Stanley Graham, Dr. J. H. Hutchison and Mr. W. Dennison, Royal Hospital for Sick Children, Glasgow, who referred these cases to me.

Dr. R. A. Kemp Harper discussed the first case shown by Dr. Rawson, and suggested that this was probably an example of an attempt at duplication of the œsophagus.

Dr. Nicholas Hajdu: To Dr. S. P. Rawson's series of cases I wish to add a case of vomiting in the neonatal period, which presented various unusual features. In this infant the co-

existence of hiatus hernia and gastric aperistalsis proved to be a lethal combination. My feeling is that the condition though rare, is not unique.

S. C., full-term female infant born by normal delivery at the Annie Macaulay Maternity Home at 5 a.m., on June 15, 1955. Apart from slight cyanosis and grunting respiration no abnormality was recorded at birth. At 12 hours the infant began to vomit green mucus and altered blood, and continued to do so for the next few days. At 24 hours meconium was passed. At 30 hours gastric lavage produced clotted blood. At 36 hours she was admitted to the Victoria Hospital for Children, S.W.3, under Dr. Ursula James, and the first films taken. At this stage one expects the whole gastro-intestinal tract to be filled with swallowed air unless intestinal obstruction is present. On the plain film (Fig. 1) there was a conspicuous dearth of gas shadows in the intestine with hardly any air in the stomach. This was surprising since the green colour of the vomits excluded œsophageal atresia, and the absence of gas distension of the stomach rendered duodenal stenosis unlikely. Opaque swallow revealed a wide patulous œsophagus, large hiatus hernia of the sliding variety and complete lack of peristaltic activity of the stomach. Clinically it had been noted that the respiratory cycle consisted of biphasic inspiration and normal expiration. During screen examination one could observe the herniated portion of the fundus passing jerkily up and down through the hiatus; the second phase of the inspiratory contraction of the diaphragm coincided with the sudden upward thrust of the hernia. The infant was wrapped in warm blankets and screened in short flashes every five to ten minutes for over an hour. No barium entered the pyloric antrum. Eventually after repeated gastric lavage the barium was brought by intubation into the pyloric antrum and it entered the duodenum by gravity (Fig. 2). Thence the barium divided: the part which had been coaxed into the duodenum was propelled normally through the small and large intestine. The part left in the stomach stayed there for over twenty-four hours (Fig. 3).

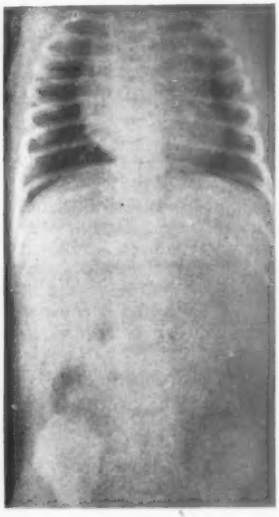

FIG. 1.—S. C., 36 hours; absence of adequate gas filling of the stomach and intestine.

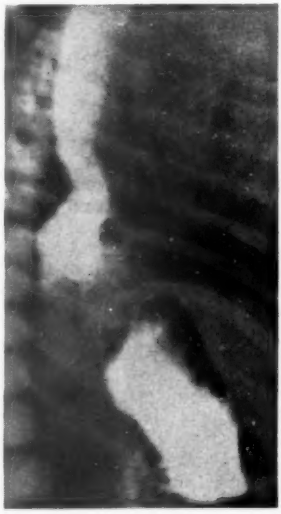

FIG. 2.—Hiatus hernia; barium gravitates into the duodenum.

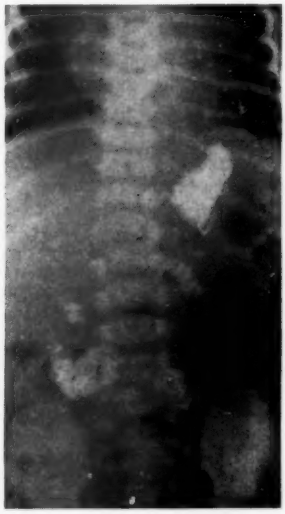

FIG. 3—Twenty-four hours later: some barium is still in the stomach.

The infant was kept on hypodermic glucose-saline and small feeds. Vomiting continued and at times there was evidence of hæmoconcentration. Of two films taken on the 6th day one showed ample air filling of the stomach and the next taken immediately thereafter showed complete disappearance of the intra-gastric air, none of which passed into the small intestine. The condition deteriorated in spite of the usual measures designed to counteract the effects of hiatus hernia. General œdema set in as a terminal event. The infant died of starvation and hypostatic pneumonia at the age of 16 days. At post-mortem the presence of a large hiatus hernia was confirmed; no organic obstruction was found in the alimentary canal.

Pathogenesis.—It was clear that the aperistaltic stomach acted as a functional obstruction. In this respect it resembled the aganglionic segment in Hirschsprung's disease. The analogy, however, could not be carried further. Dr. N. F. C. Gowing of St. George's Hospital, who was approached on the subject, was able to demonstrate intact ganglion cells in the gastric wall, in the nearest sympathetic ganglia and in serial sections of the brain. The neurogenic theory had therefore to be abandoned in favour of a mechanical one. H. H. Nixon has

shown that within the gut a minimum pressure must exist below which intestinal loops cannot start peristaltic movements. We see no reason to assume that conditions are different in the stomach. One may therefore postulate that an intragastric threshold pressure is necessary for the propulsion of the gastric contents. If the large hiatus hernia prevents the stomach from building up the required pressure, complete gastric aperistalsis, as observed, will be the direct result.

Diagnosis and treatment.—The only other condition in which there is absence of gas shadows in the stomach and intestine, is atresia of the œsophagus without lower tracheobronchial fistula. In these cases the clinical picture is different. The absence or instability of the gastric air bubble should make one think immediately of hiatus hernia. I should like to make a plea to pædiatric radiologists to search their files for cases of neonatal death associated with hiatus hernia. Do the films show absence of the gastric air bubble? If so, it would constitute a valuable diagnostic sign, defining a group of poor prognosis in whom expectant treatment is fraught with great dangers. More active treatment, such as intraduodenal feeding through a gastrostomy tube or immediate surgical reduction of the hiatus hernia would appear indicated. In contrast it may be found that those cases of hiatus hernia who present few clinical problems retain their gastric air bubble and show no disturbance of gastric peristalsis. One may hope that by collating the experiences of different observers a rare condition of this kind will eventually be fully understood.

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X-ray Manifestations of Early Malignant Gastric Ulceration

By G. A. S. LLOYD, B.M., B.Ch., D.M.R.D., F.F.R.

THE object of this paper is to describe the X-ray appearances found in a series of cases of early malignant gastric ulcers, recently investigated at the London Hospital. The approach to the subject was entirely retrospective, in that it was based on a review of all the cases of gastric carcinomata which were confirmed by gastrectomy in the years 1949–1953 inclusive. There were in all 254 cases, and we were able to examine the radiographs of 213 of these.

In the investigation we were interested only in those cases which had proved difficult from the radiologist's point of view, and so we eliminated all those which had been diagnosed immediately after the first barium meal examination, and confined our study only to the cases in which there had been a delay of more than two months from the first barium meal to the time of gastrectomy. In other words we eliminated all the radiologically obvious carcinomata and concentrated on the cases showing minimal changes, in which a diagnosis had not been made immediately. Examining the films of these, we found that they fell into 4 groups:

(1) Neoplasms, involving the cardia.
(2) Pre-pyloric growths.
(3) Neoplasms presenting as a stomach deformity only.
(4) Neoplasms presenting as lesser curve ulcers.

The last group was by far the largest, being some 26 in number, and I shall discuss only this group.

All of them had been examined at least twice by barium meal, so that it was possible to review their films serially, and we were able to determine both the earliest changes visible on the films and the manner in which the ulcers had developed. We found that, in general, the malignant ulcers had presented either as small flat or plateau ulcers, or as small ulcers usually conical in shape, closely simulating a benign ulcer. In addition, there was a small group of 3 cases which had presented radiologically as a benign ulcer proximal to, but entirely discrete from, a gastric neoplasm, that is to say, that there was both a neoplasm and a benign ulcer in the same gastrectomy specimen, but quite separate.

The plateau ulcer or "niche en plateau" has been described before, notably by the French writers Gutmann *et al.* (1939), Peristiany (1937) and Ledoux-Lebard (1940). Kirklin (1934) has also described a similar type of lesion. It is essentially a shallow projection with a flat, or slightly convex outer surface and usually measuring between 1 and 2 cm., although it can sometimes be larger than this (Figs. 1 and 2). At its inception, it is usually found to project beyond the line of the lesser curvature. The only distinctive feature of the plateau ulcer, apart from its shape, is the presence of an intra-luminal meniscus. In our cases we were able to detect a meniscus in no less than 8 out of the 13 which presented in this way, and it must be regarded as an important additional sign. Obviously a small ulcer of this shape can be easily confused with a peristaltic wave, or mucosal fold on the

FIG. 1.—An example of the flat or plateau type of malignant ulcer.

FIG. 2.—Small plateau ulcer on the lesser curvature of the stomach.

FIG. 3.—Plateau ulcer with a shallow filling defect, and embedded within the stomach contour. It has the serrated margin characteristic of this type of malignant ulcer.

FIG. 4.—Small conical type of early malignant ulcer.

radiograph, and it is not surprising to find that the majority in our series were not diagnosed as ulcers originally.

In summary then these ulcers are characterized by their flat shape, the presence of a meniscus which is intra-luminal, and from the practical point of view they are sometimes difficult to distinguish from normal variations in the stomach contour.

As the plateau ulcer develops, it becomes progressively more intra-luminal in position. The crater becomes larger and the meniscus wider and more obvious. It is then essentially a flat ulcer within a filling defect, and corresponds to the appearance called by the French writers the "niche en plateau encastrée", i.e. a flat ulcer embedded within the stomach contour (Fig. 3). Thus the usual evolution of these ulcers is from a simple flat projection into a similar projection, but embedded in a shallow filling defect and becoming progressively intra-luminal in position. When the filling defect becomes larger still, the lesion is then essentially an ulcerated mass and the diagnosis is quite obvious.

The second way in which these neoplasms presented was as a simple-looking ulcer, projecting further from the stomach outline than the first type, and usually conical in shape (Fig. 4). The main radiological problem in this variety is to distinguish them from the benign gastric ulcer, and in our series the majority were originally thought to be benign. The possibility of malignancy was only suggested when either the ulcer began to acquire a filling defect, or when it failed to respond to medical treatment. Some of these cases had very long histories with slow progression of the lesion and, obviously, into this group fall those ulcers which are considered to be malignancy supervening in a chronic benign ulcer. As a matter of fact in only 2 cases did the pathologist's report suggest this, but it was interesting to note that these were the only 2 in the series which diminished in size whilst under observation. When these conical ulcers acquire a surrounding filling defect, the diagnosis may be suggested on the strength of this, since the ulcer becomes intra-luminal in position (Fig. 5).

FIG. 5.—Small malignant ulcer within a shallow filling defect. The "niche banale encastrée" of the French writers.

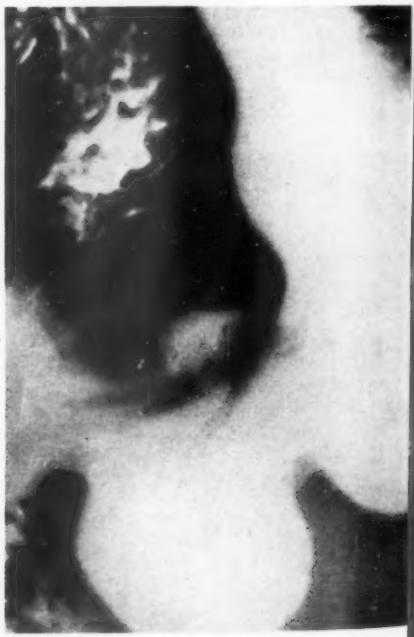

FIG. 6.—Malignant ulcer showing converging mucosal folds.

Here again then the evolution of the ulcer is from a simple projection to a projection within a filling defect and this, of course, is the progression to be expected if, as it would

seem, some of these cases were initially benign ulcers which subsequently developed malignant change.

A small group of cases presented as a benign ulcer on the lesser curvature in association with, but discrete from, a malignant neoplasm of the stomach. There were three instances of this association demonstrated in our series, and probably a fourth, which could not be confirmed pathologically. In 2 cases the neoplasm was a carcinoma and in the other it was diagnosed histologically as a lymphosarcoma. In each instance the malignant ulcer was located at, or distal to, the incisura angularis, while the proximal benign ulcer was found on the vertical section of the lesser curvature, above the angulus.

Classical X-ray criteria of malignant ulceration as applied to the lesions in this series.—Brief mention must be made of the size and position of the ulcers. The first criterion, that of the size of the ulcer, could not be fairly applied to this group of cases since they were all too early for this sign to have any bearing on the problem. As regards the position also, it was felt that no statistically valid conclusions could be drawn from a series of 26 cases. However, there are two other signs which require more detailed consideration. The first is that of the position of the ulcers with respect to the line of the lesser curvature, i.e. whether they were intra-luminal or extra-luminal. Only 25% could be considered intra-luminal originally, although many more became so at a later examination. This is not surprising if, as it would appear from this investigation, that the usual course of evolution of these lesions is for them to begin as a projection only, which later acquires a filling defect. The conclusion is then, that if a small ulcer is extra-luminal in position, it should not be considered benign because of this. A malignant ulcer only becomes intra-luminal when the process is relatively advanced, and indeed the growth may metastasize before this sign becomes positive.

The second criterion, which is quoted in many of the standard textbooks of radiology, is that of the convergence of folds to the crater. It is said that in simple chronic ulcers the rugæ tend to converge to the crater, whilst in malignant ulcers they are said to be interrupted without converging. Many of these malignant ulcers showed converging folds, which were uninterrupted to the edge of the crater (Fig. 6) and what is most significant is that the X-ray reports repeatedly quoted this in support of their being benign lesions. The sign is therefore, in practice, most unreliable in the early lesion. In many cases, the carcinomatous infiltration around a malignant ulcer is submucous, and the earliest changes will be shown radiologically as a thickening, or irregularity, in the mucosal folds; or they may be separated by wider spaces than usual. These changes commonly precede the obliteration of the folds. On the other hand, peri-ulcerous œdema in a simple peptic ulcer may obliterate the folds to simulate the classic concept of the malignant ulcer. All that the presence of folds demonstrates is that the surface of the mucosa is intact. It does not exclude the presence of submucous infiltration, which may be shown either by a profile filling defect, or by qualitative changes in the mucosal fold pattern around the crater.

It may be concluded that the classical criteria of malignant ulceration are of little value in reaching a diagnosis in the early stages. The shape of the ulcer crater is far more important. I have shown that the early malignant ulcer usually presents in two ways; either as a conical ulcer or as a plateau ulcer. In the conical ulcers a tentative diagnosis is only possible after consideration of the behaviour of the lesion under medical treatment, since the lesion so closely simulates a benign ulcer. On the other hand, the shape of the plateau niche is unlike that of a benign ulcer and the appearances should always be considered very suggestive of malignancy, especially if it is possible to demonstrate an intra-luminal meniscus or collar to the crater. The embedded plateau ulcer—the niche en plateau encastrée—is nearly always malignant; only rarely is such an appearance mimicked by a benign ulcer. It remains true, however, that an absolute diagnosis is not always possible in the early case, and the diagnosis from a benign ulcer must be made in terms of probability. An accurate estimate of the chances of malignancy on a given ulcer shape could only be furnished by an extensive statistical survey of a large series of both malignant and benign gastric ulcers.

The case material used in this publication is taken from a paper on "Malignant Gastric Ulceration" written by the author, in collaboration with Dr. J. L. Morris, and published in the *Journal of the Faculty of Radiologists* (1956), **7**, 207.

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Some Difficulties in the Diagnosis of Carcinoma in the Region of the Cardia

By CONWAY DON, M.B., B.S., M.R.C.P., D.M.R.D., F.F.R., and D. J. L. MURPHY, B.Sc., M.B., F.R.C.S.

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THE routine methods of investigating lesions in the region of the cardia are barium swallow and meal, and œsophagoscopy with biopsy. A series of cases seen recently at University College Hospital is presented to illustrate some of the limitations of these methods.

The main radiological difficulty in this series was not that radiology revealed no lesion but that it showed an apparently benign lesion which could have accounted for the patient's symptoms. This is due to the fact that carcinoma of the cardia may be associated with a benign lesion (hiatus hernia) or may simulate one (achalasia of the cardia, or compression by the aorta). It may also be difficult to localize the lesion to the cardia as, owing to its association with hiatus hernia, it may be at any level from the diaphragm to the aortic arch. In Cases I–V, the difficulty arose through this association.

Case I.—This patient, a man of 50, had a barium swallow at University College Hospital in September 1954 for a three months' history of epigastric and lower sternal pain on swallowing. (Fig. 1). This showed a small but irreducible hiatus hernia; the œsophagus and cardia were pliable

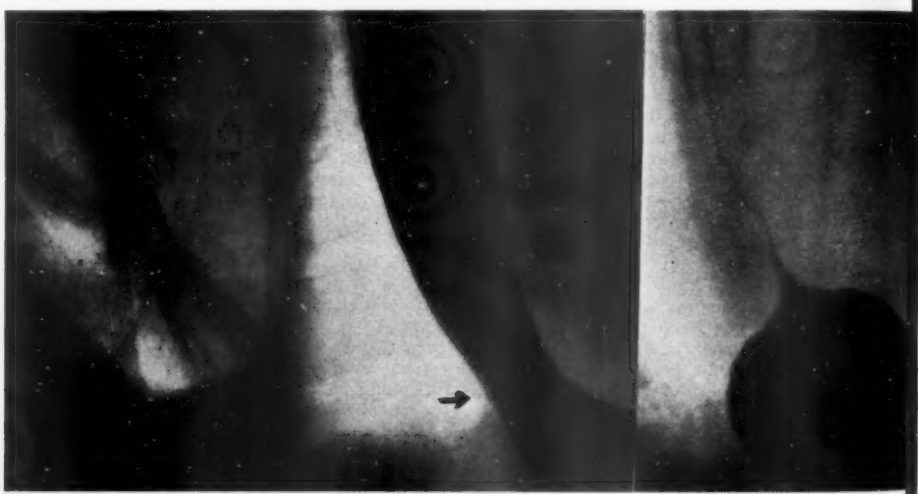

FIG. 1.—September 1954: Hiatus hernia with possible small peptic ulcer of cardia demonstrated.

and expanded and contracted freely, and there was considered to be no evidence of neoplasm. There was a small projection from the posterior aspect of the lower œsophagus, which was reported as a probable peptic ulcer associated with a hiatus hernia.

This accorded well with the clinical picture, and it was decided that œsophagoscopy was not indicated unless the patient's symptoms failed to respond to medical treatment. The pain was alleviated by treatment, and after a while he ceased to attend the out-patient department.

Nine months after first attending, he was admitted to another hospital, having by now developed dysphagia. A barium swallow was interpreted as showing a small hiatus hernia with a stricture above it, presumably due to reflux œsophagitis. Biopsy of a neck gland, however, showed a squamous carcinoma, and a third barium swallow shortly after showed an obvious filling defect in the supradiaphragmatic pouch.

Œsophagoscopy showed a stricture which, on biopsy, was malignant, and laparotomy revealed an inoperable mass involving the lower œsophagus and the fundus of the stomach.

In this case, therefore, there was a delay of nine months in the diagnosis of a carcinoma involving the lower œsophagus and fundus. The initial delay was largely due to the radiological demonstration of an apparently benign lesion, and partly to the omission of œsophagoscopy.

Case II.—This woman of 73 was admitted to another hospital in October 1954 with a history of attacks of lower sternal pain on swallowing for many years, with the recent onset of slight dysphagia and loss of weight. Her barium swallow (Fig. 2) showed a large fixed para-œsophageal hernia,

FIG. 2.—Barium swallow showing large fixed para-œsophageal hernia; no evidence of carcinoma. Co-existing carcinoma of supradiaphragmatic stomach found at operation.

and œsophagoscopy was not considered necessary. She was treated medically as an in-patient with response of symptoms, bnt was readmitted for further medical treatment some months later.

Seven months after her initial investigation, she was referred for a surgical opinion to University College Hospital, as she was not improving. A further barium swallow was again considered to show only a large fixed para-œsophageal hernia, with no evidence of any other lesion. Œsophagoscopy was performed for the first time, and the only abnormality revealed was that the lower end of the œsophagus was lined by gastric mucosa. The mucosa of both gullet and stomach appeared healthy. Biopsy showed no evidence of malignancy.

The lesion therefore appeared to be an uncomplicated hiatus hernia, and an operative repair was attempted. At operation, however, an inoperable carcinoma of the supradiaphragmatic portion of the stomach involving the cardia was found.

In this case, therefore, the radiological findings of a benign lesion (a fixed para-œsophageal hernia) resulted in a delay of seven months in the diagnosis of an associated carcinoma of the stomach, which was found incidentally at operation to repair the hernia. Œsophagoscopy and biopsy proved misleading.

Case III.—This woman aged 73 attended the E.N.T. department of another hospital with a six months' history of dysphagia; she was able by then only to swallow liquids. Barium swallow (Fig. 3A) showed a nearly complete obstruction of what appeared to be the mid-third of the œsophagus. Judged on radiological characteristics, the stricture was benign.

She was transferred to the E.N.T. department of University College Hospital for further investigation. At œsophagoscopy, a stricture was found and dilated, and a Ryle's tube passed to enable the patient to be fed. There was no evidence of malignancy at œsophagoscopy, and biopsy from the edge of the stricture showed gastric mucosa with active inflammation.

It was thought, therefore, that the patient probably had a benign stricture associated with a hiatus hernia, and this view was confirmed when barium introduced into the stomach through the Ryle's tube showed a hiatus hernia (Fig. 3B). The patient's symptoms, however, failed to respond

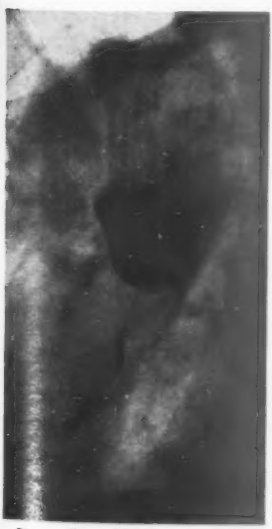

FIG. 3A.—Barium swallow showing tight stricture of œsophagus, radiologically benign.

FIG. 3B.—Barium introduced through Ryle's tube showing presence of hiatus hernia. Stricture found to be due to carcinoma of the cardia.

to repeated dilatation, and further biopsy revealed an adenocarcinoma. At thoracotomy, an ulcerating carcinoma of the cardia 3 cm. long was removed.

In this case, then, radiology revealed only a benign lesion, and œsophagoscopy initially confirmed it; the associated carcinoma was only revealed by a second biopsy after the failure of conservative treatment.

In this connexion, it may be pointed out that Allison (1948) warns that radiologically it may be very difficult to distinguish a benign stricture above a hiatus hernia from a carcinoma; and Pattinson and his colleagues (1955) point out that even repeated

FIG. 4A (*Case V*).—Irregular filling defect apparently in lower end of œsophagus: lesser curve normal. Patient supine.

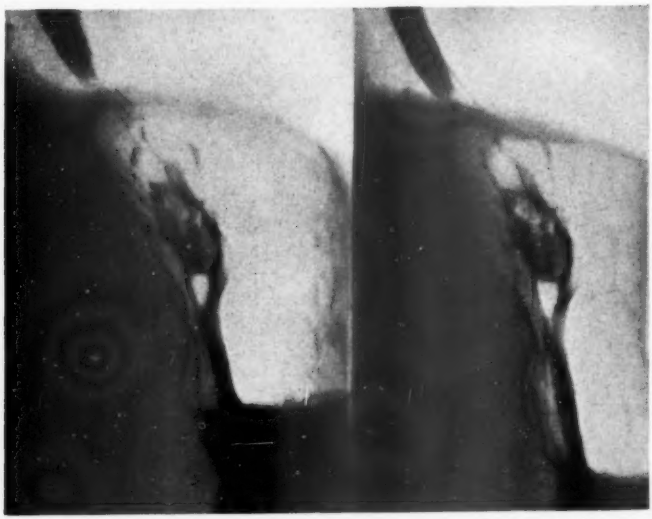

FIG. 4B (*Case V*.).—Irregular filling defect now of lesser curve of stomach: lower œsophagus normal. Patient erect.

œsophagoscopy and biopsy of these lesions may fail to show any evidence of malignancy.

Case IV (*Not illustrated*).—This patient, a man of 76, was admitted as an emergency with dysphagia causing complete obstruction. A barium swallow showed an obviously malignant stricture of what was taken to be the mid-œsophagus. The patient died after emergency jejunostomy, and at post-mortem the carcinoma was found to encircle the cardia, the stomach being herniated into the thorax. Review of the films showed no plain film evidence of the hiatus hernia. Radiography therefore showed a carcinoma wrongly diagnosed as arising in the mid-third of the œsophagus, owing to the presence of an associated hiatus hernia.

Case V.—This man, aged 64, attended University College Hospital with a history of dysphagia for three months. Previous barium swallows at two other hospitals had shown no abnormality, but the stomach did not appear to have been examined. Barium swallow films at University College Hospital (Figs. 4A and B) showed an apparent filling defect in the lower 4 cm. of the œsophagus extending into the cardiac portion of the stomach, and was considered to show an œsophageal neoplasm extending into the stomach.

It was expected that this lesion would be easily visible on œsophagoscopy. but, in fact, no abnormality was detected, and doubt was expressed about the radiological findings. The reason for this discrepancy, which was not fully appreciated at the time, can be seen from the illustrations. In Fig. 4A the patient is supine, and the filling defect appears to be entirely in the lower œsophagus; the lesser curve appears normal. In Fig. 4B, the patient is erect, and the filling defect is on the lesser curve; the œsophagus is normal. The filling defect in fact herniates above the diaphragm when the patient is supine, and reduces in the erect position. Presumably, at œsophagoscopy the lesion had prolapsed below the diaphragm ahead of the œsophagoscope and slipped down the lesser curve just out of the narrow range of vision of the œsophagoscope. This would also account for the negative findings at the previous barium swallows, which had been conducted in the erect position, and in which the stomach had not been examined.

A further barium swallow showed an unchanged appearance, and despite the negative œsophagoscopy findings, laparotomy was undertaken, and an ulcerated carcinomatous plaque 3 cm. by 6 cm. was found in the cardia, extending predominantly down on to the posterior aspect of the lesser curve.

In this case, then, after two negative barium swallows, a swallow and meal revealed a carcinoma of the cardia which œsophagoscopy failed to confirm, owing to reduction of an unrecognized hiatus herniation of the carcinoma.

An additional point of interest in this case is that Smithers (1955) considers that there is a significant relationship between hiatus hernia and carcinoma in the region of the cardia, and postulates that this may in part be due to the carcinoma irritating the lower end of the œsophagus and producing the hiatus hernia (in those predisposed) by spasm of the longitudinal muscle of the œsophagus. It is possible that this case, in which an early carcinoma of the cardia is associated with an incipient sliding hernia, is in fact an instance of this mechanism at a very early stage of its development.

That carcinoma involving the cardia may simulate achalasia, despite careful radiography and œsophagoscopy, is well known; it has recently been emphasized by Anderson and Kelly (1954). The following case is an example of this.

Case VI.—This man aged 70 was investigated extensively at another hospital for dysphagia and pain at the lower end of the sternum, three barium meals and an œsophagoscopy being performed. This barium swallow and meal showed a smooth tapering obstruction of the œsophagus indistinguishable from achalasia, and there was no evidence of malignancy in the œsophagus or stomach radiologically or on œsophagoscopy. He was considered to have an achalasia and treated medically.

Eight months later, as he had not improved, he was referred to University College Hospital. Barium swallow again showed an apparent achalasia, and œsophagoscopy with biopsy of the narrowed segment showed no evidence of carcinoma. Bougies passed into the stomach met with no resistance to suggest a growth. After dilatation of the stricture, barium passed more easily into the stomach, and a further barium meal (the fifth) was now reported as being suspicious of a fundal neoplasm. An air insufflation was therefore performed and air passed freely around the lower end of the œsophagus, the cardia and the fundus, and there was nothing to suggest a neoplasm.

The patient was therefore regarded as a case of achalasia, and treated by a course of dilatation. Eventually, as his symptoms did not respond adequately, a Heller's operation was decided upon to relieve his achalasia, and, at operation, a diffusely-infiltrating and inoperable carcinoma of the stomach involving the cardia was found.

In this patient, therefore, five barium meals (at two different hospitals), an air insufflation and repeated œsophagoscopies with biopsy led to the diagnosis of achalasia of the cardia, and there was a delay of fifteen months in the diagnosis of a carcinoma of the stomach involving the cardia.

It is not uncommon for the lower end of the œsophagus to appear compressed by the aorta, and some authors (e.g. Mucklow and Smith, 1954) consider this to be a cause of symptoms. The following case illustrates an apparent instance of this.

Case VII.—This man of 72 had a barium swallow at University College Hospital for an eight-months' history of regurgitation of food without dysphagia (Fig. 5). The swallow showed a smooth

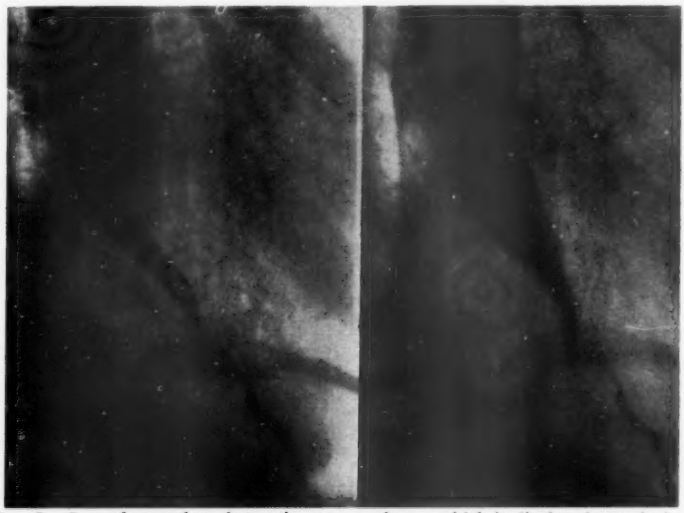

FIG. 5.—Smooth tapering obstruction to œsophagus which is displaced anteriorly and apparently compressed by descending aorta: no radiological evidence of carcinoma. Due in fact to carcinoma of cardia.

narrowing of the œsophagus occurring just where it was crossed by an unfolded and calcified descending aorta; it appeared possible that the œsophagus was compressed between the aorta and the heart, which was displaced backwards by a depressed sternum.

A second swallow was performed specifically to examine this possibility, and the report stated that "the walls of the œsophagus appeared to be completely flaccid, and, in spite of prolonged examination, there was really nothing to suggest intrinsic organic disease"; compression was, in fact, considered to be the cause of the narrowing.

FIG. 6.—Third barium swallow, eleven months after first, showing extensive irregular filling defect in lower œsophagus.

As a precaution, however, the patient was œsophagoscoped. Although marked aortic pulsation was seen just above the cardia, there was no corresponding œsophageal narrowing. There was no macroscopic evidence of carcinoma, but a biopsy from the region of the cardia showed an anaplastic carcinoma. The patient died from a chest infection, and at autopsy there was an almost complete stricture of the lowest 3 cm. of the œsophagus from a carcinoma of the cardia.

In this case, then, despite particularly careful radiological examination an obstruction of the lower œsophagus was considered to be benign, but precautionary œsophagoscopy revealed a carcinoma.

Case VIII.—This patient had a barium swallow in January 1954 for a history of retrosternal pain radiating to the right scapula, and related initially to swallowing. No abnormality was revealed. 5 months later, as the patient's symptoms persisted and various other investigations had been negative, a second swallow was performed and again no abnormality was found. It was considered that a negative examination five months after the first rendered a carcinoma most unlikely, and the patient's pain was attributed to severe degenerative changes in the thoracic spine. In December 1954, however, a third barium swallow showed an obvious fungating carcinoma (Fig. 6). At operation, a large anaplastic carcinoma of the œsophagus was resected.

In this case, reliance on two negative barium swallows without œsophagoscopy resulted in a delay of eleven months in the diagnosis of a carcinoma of the lower end of the œsophagus.

Conclusions.—(1) Radiological technique must be meticulous, and the gastric as well as the œsophageal aspects of the cardia must be carefully examined.

(2) One must not be misled by the fact that carcinoma of the cardia may be accompanied by, or may simulate, a benign lesion which could account for the symptoms.

(3) No patient with a possible carcinoma of the cardia can be regarded as properly investigated until œsophagoscopy has been performed.

(4) Despite benign findings on X-ray examination and œsophagoscopy, the clinician must be prepared on any clinical suspicion of carcinoma to resort to immediate surgical exploration.

Our thanks are due to Professor R. S. Pilcher and Dr. S. Cochrane Shanks, for their assistance in the preparation of this paper.

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Radiological Manifestations of Hyperparathyroidism

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HYPERPARATHYROIDISM has been diagnosed more frequently during the past few years than ever before and relatively large series of cases have been reported in the literature during the past three years mainly from the Mayo Clinic and from Stockholm.

Cases may remain undiagnosed for some considerable time often due to the fact that local disease processes are treated and a general systemic disease is overlooked.

The radiologist can be of considerable help in the diagnosis of cases of hyperparathyroidism, particularly in those showing generalized bone disease and also in patients showing renal calculi.

Dent and Hodson (1954) and also Hellstrom (1954) indicate that approximately 20–30% of cases of primary hyperparathyroidism may show skeletal changes, whereas more than 50% of Hellstrom's series of 50 cases had radiological evidence of renal calculi or calcifications. However, even although approximately only a third of cases have skeletal changes, nevertheless, radiological investigation may first bring the diagnosis to light. In a group of 14 cases which I have seen in Edinburgh, a greater proportion—78%—showed skeletal changes and 50% had renal calculi demonstrable on X-ray examination.

Clinically, primary hyperparathyroidism may present in several ways. Hellstrom (1954) found that renal and skeletal symptoms predominated, but he also found a fair proportion of cases complaining mainly of abdominal symptoms, headache and general weakness. Patients may thus be referred for X-ray examination with a fairly wide variety of provisional clinical diagnoses.

From the radiological aspect in the adult, there are no distinguishing features between primary hyperparathyroidism and secondary hyperparathyroidism as found in renal osteodystrophy, and in a case with advanced renal disease the differentiation may be well-nigh impossible from the clinical aspect.

The manifestations of hyperparathyroidism are described in considerable detail in the radiological literature and all radiologists are familiar with these, but in view of the unusual way in which cases may present, it is essential for the radiologist to be continually on the alert when studying any X-ray film no matter what the clinical diagnosis may be.

ILLUSTRATIVE CASES

Case I.—A married woman, aged 49, who, after a hysterectomy for menorrhagia in January 1953, developed marked weakness and malaise and had frequent vomiting. In August 1953 she was treated for anæmia and in November 1953 was admitted to hospital with recurrence of anæmia.

Investigation included a barium enema examination which was normal, but the lumbar spine showed quite marked generalized osteoporosis with ill-defined trabeculæ. Further radiographs of the skull showed punctate, granular osteoporosis and the hands (Fig. 1) showed subperiosteal erosions of the phalanges, particularly the middle phalanges. Similar erosions were seen in the feet and ischio-pubic rami. No renal calculi were demonstrated. Blood chemistry showed an elevated serum calcium and phosphorus. A nodule could be palpated in the right lower pole of the thyroid. At operation, this proved to be a parathyroid adenoma.

Post-operatively, the blood chemistry and skeletal changes returned to normal.

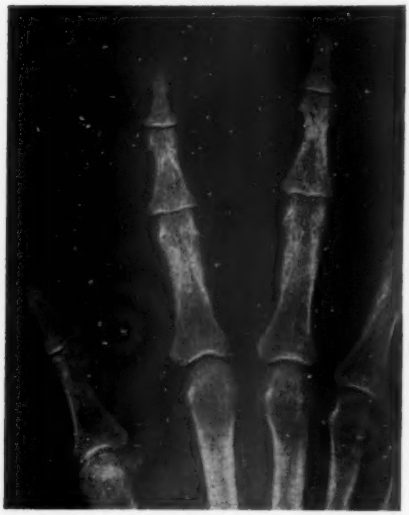

FIG. 1 (*Case I*).—Subperiosteal erosion of phalanges, particularly middle phalanges.

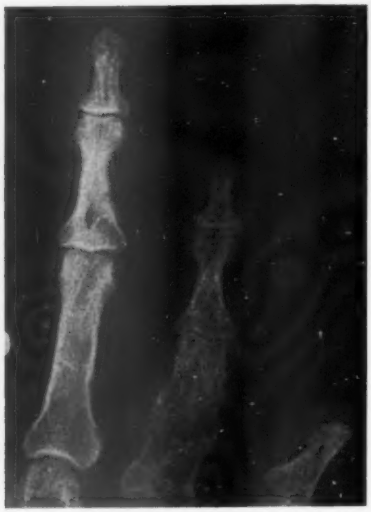

FIG. 2 (*Case II*).—Subperiosteal erosion of phalanges and cyst formation in the second proximal phalanx.

Case II.—A married woman, aged 64, was admitted to hospital in December 1952 with right-sided abdominal pain, but no vomiting or urinary symptoms. She also gave a history of "arthritis" for ten years. Radiographs of the abdomen and pelvis showed a small right renal calculus and diffuse skeletal osteoporosis and cystic changes. The hands (Fig. 2) showed typical subperiosteal erosions but also cystic changes in the phalanges. The feet showed similar changes with cysts in the metatarsals and associated stress fractures. Blood chemistry showed elevated serum calcium and low serum phosphorus. The neck was explored and a tumour 3 × 2 cm. was removed from the right lower parathyroid area, which proved to be a simple adenoma. After a month there was considerable general improvement and after a year bone density was markedly improved and bone regeneration had taken place in the cystic areas.

Case III.—A married woman, aged 40, who was admitted to hospital in September 1951, complained of a swelling of her right leg of six months' duration. The swelling was slightly tender and the leg ached. Radiographs showed two cystic areas in the right tibial shaft (Fig. 3), together with osteoporosis and some subperiosteal erosion of the medial aspect of the upper end of the tibia. The abdomen (Fig. 4), showed large multiple bilateral renal calculi in rotated, probably horseshoe, kidneys. On intravenous urography, there was very poor renal function. A film of the thoracic inlet showed a soft tissue opacity on the right side of the trachea and subperiosteal erosion of the inferior aspects of the sternal ends of both clavicles. Changes typical of hyperparathyroidism were noted in the skull. Blood chemistry showed considerable elevation of serum calcium and a low serum phosphorus.

At operation, four large tumours were found and removed, 71 grams in all of parathyroid tissue. This is slightly more than the greatest amount previously reported (Paul, 1931). All four tumours showed changes of primary parathyroid hyperplasia with the cells exclusively of the water-clear type.

Post-operatively, the blood chemistry returned to normal as did the general skeletal changes.

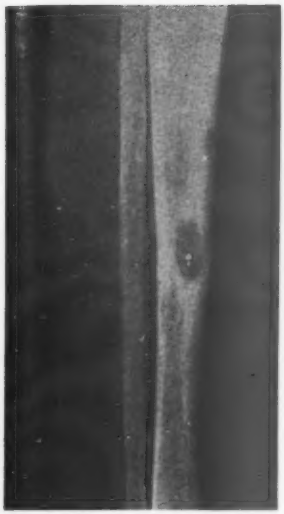

FIG. 3 (*Case III*).—Cystic change in mid-shaft of tibia.

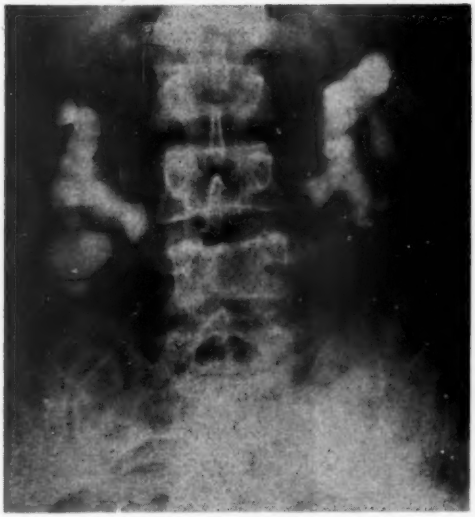

FIG. 4 (*Case III*).—Multiple, bilateral renal calculi in rotated, probably horseshoe, kidneys.

Case IV.—A married woman, aged 70, was admitted to hospital in October 1955, complaining of breathlessness and increasing tiredness for the previous six months. She had apparently been fairly well until two years before, when she began to have pains in knees, elbows and legs and had difficulty in walking. She had noticed some frequency of micturition for the previous eight to ten years and had some degree of thirst. There was no history of renal disease. On examination, she was found to be anæmic and her hands showed a rather unusual form of finger clubbing with beak-like nails.

Radiographs of both hands (Fig. 5), showed subperiosteal erosion of the phalanges and unusual

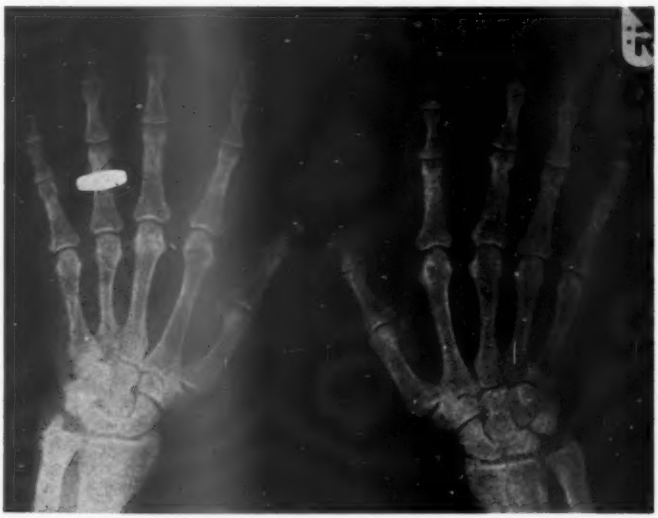

FIG. 5 (*Case IV*).—Partial asymmetrical absorption of terminal phalanges with associated expansion of the pulp of the fingers.

changes in the terminal phalanges, which were partly absorbed leaving osteoporotic tufts and resulting in over-all shortening. A bulbous appearance of the soft tissues was noted where the shortening was greatest. Typical hyperparathyroid changes were seen in the skull (Fig. 6). Other

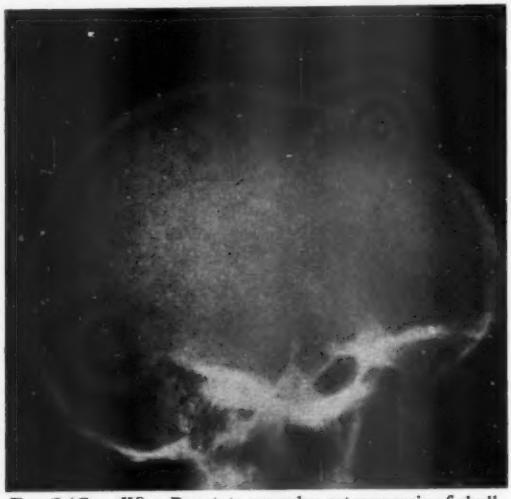

FIG. 6 (*Case IV*).—Punctate granular osteoporosis of skull.

radiographic findings were subperiosteal erosions of the ischio-pubic rami and medial aspects of the upper ends of the tibiæ and stippled calcifications in the left kidney. All these changes would be consistent with a diagnosis of hyperparathyroidism, but whether primary or secondary is very difficult to decide. Blood chemistry showed serum calcium and phosphorus within normal limits. Calcium balance tests were likewise within normal limits. Renal function tests, however, showed a urea clearance of only 30% of normal.

Absorption of terminal phalanges with finger clubbing is not mentioned as a usual finding in hyperparathyroidism. Snapper (1949), Schneider (1953) and more recently Souders and Manuell (1954) have described similar changes in primary hyperparathyroidism. Clinically, the clubbing is not of the usual type; the pulp of the fingers appears rather flabby and the tips of the fingers are shortened. Snapper and Souders and Manuell suggest that the clubbing in their cases is due to loss of skeletal support or that there is a specific soft tissue reaction to the disease in this area. The theory of loss of skeletal support seems to be borne out in the radiograph of the hands (Fig. 5), as the clubbing is most marked where the shortening of the terminal phalanges is greatest. Since this paper was prepared further clinical investigations suggest that this case is one of primary hyperparathyroidism with associated renal advanced disease.

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Section of Experimental Medicine and Therapeutics

President—E. E. Pochin, M.D., F.R.C.P.

[*October* 11, 1955]

DISCUSSION ON HYPERSENSITIVITY AND THE COLLAGEN DISEASES

Dr. E. G. L. Bywaters (Postgraduate Medical School of London; Canadian Red Cross Hospital, Taplow):

What is the Evidence of Hypersensitivity in the Pathogenesis of the So-called Collagen Diseases?

What is the evidence for the widespread assumption that hypersensitivity is important in the pathogenesis of the "collagen diseases"? They are a group of syndromes of whose nature we are ignorant, but whose manifestations are located largely in connective tissue. There are many substances in connective tissue much more reactive than collagen and there is yet no convincing evidence that the protein collagen itself is involved. The term was invented by Klemperer to cover diseases with fibrinoid changes seen in so many different conditions, from peptic ulcer to malignant hypertension. Even in lupus erythematosus, the prototype as it were, the name "collagen disease" has seen better days, and Klemperer himself now feels that the fibrinoid of lupus erythematosus is probably derived from a disorder of nucleic acid breakdown via the L.E. cell and the hæmatoxylin body. However, the term usually includes:

Rheumatoid arthritis and ankylosing spondylitis, polyarteritis nodosa, generalized lupus erythematosus, dermatomyositis, scleroderma, rheumatic fever, glomerulonephritis, Henoch-Schönlein purpura, erythema nodosum, and others at will.

Each of these is a real and separate clinical entity—hybrids being usually more apparent than real. Many clinical and pathological changes are common to the group as a whole and it might be supposed that some of the more nearly related of these conditions may have certain steps in the pathogenesis in common and our question is—"Does one of these steps involve the mechanisms of hypersensitivity?"

I shall only consider here hypersensitivity in the immunological sense as a state of reactivity to antigen or haptene due to antibody—although in many instances we cannot find the antibody, do not know the antigen and merely suppose that what we see is due indirectly to the union of these supposititious substances.

You cannot have hypersensitivity without something to be hypersensitive to. We recognize it for certain only in relation to this precipitating or causative factor and then only if this reaction meets certain criteria, one of which is that most (normal) people do not react to that substance in such proportions or in such a way. In the allergic person the response is specific to the antigen (although even this may change in the course of time). The reaction occurs to a dose of antigen below the pharmacological level and is different from the pharmacological or toxic reaction in character. The reaction pattern is stereotyped and within certain limits does not depend upon the nature of the antigen (although its localization may do so). There is no reaction on first exposure: sensitization takes time and finally antibody must be demonstrated either in cells or serum.

Can we recognize such a state without knowledge of a precipitating or causal factor? We can, but only by analogy. This happened with asthma. Like clinical pictures, we say, are due to like causes and therefore will respond to the same treatment.

There are three main types of clinically recognized hypersensitivity: *firstly* asthma, hay fever, infantile eczema, and hives, constituting the well-known naturally developing sensitivities; *secondly*, serum sickness, contact dermatitis and drug allergy. *Thirdly, bacterial allergy*, our knowledge of which is still in its infancy. *In addition* to these, there is the concept of *auto-immunization*, which is thought to be a possible factor in acquired hæmolytic anæmia, and perhaps other diseases, based largely on the analogy with the

findings in acquired Rhesus sensitization. (Yet only 2–4% of Rhesus-negative people exposed to the antigen produce clinical disease.)

Are there analogies between any of the collagen diseases and any one of these four types of hypersensitivity strong enough to make us think that the "collagen disease" is due to hypersensitivity? Let us start with the study of *erythema nodosum*.

This is a fairly stereotyped reaction pattern developing in response to various infections by bacteria, fungi, &c. The most common organism in this country is *Mycobacterium tuberculosis:* it develops after a period of sensitization and resembles fairly closely the Mantoux-positive reaction. We suppose that in the affected sites, antigen has been deposited and when antibody-producing cells appear, they react with antigen locally. Similar eruptions are also seen in patients with negative Mantoux reactions and sarcoidosis, sometimes after streptococcal infections, sometimes in ulcerative colitis, &c. The attack is self-limited, may recur after a lapse of time on further exposure and may be reproducible on injection of antigenic constituents: only a small proportion of people exposed to tuberculosis, streptococci, ulcerative colitis, &c., develop this lesion. In all these respects, therefore, it resembles the classical allergic diseases.

Henoch-Schönlein purpura is a similar disease, sometimes precipitated by streptococci, sometimes by food allergy, sometimes without a known causal factor. Like erythema nodosum, it involves skin and joints; sometimes fibrinoid lesions of vessels are seen, sometimes glomerulonephritis. It affects only a very few of those who develop streptococcal infection, and runs a self-limited course.

Rheumatic fever and acute glomerulonephritis are again associated with Group A beta hæmolytic streptococcal infection, the latter with specificity limited to a few types. They occur only in a small proportion of exposées and are comparatively self-limited diseases (apart from the results of scarring). Antibodies other than those occurring in any streptococcal infection have not been consistently found, although various authors such as Cavelti, Rejholec and Wagner, Lange *et al.*, have reported antimyocardial or antirenal antibodies using the collodion particle technique. This technique is difficult both to interpret and to reproduce, but the theory of auto-immunization seems as good as any at the moment. However, we still do not know why some develop rheumatic fever and others do not. While heredity plays some part, and repeated exposure to streptococci is known to be required, some other factor is necessary. This unknown may be responsible for the fall in severity and incidence of rheumatic fever since 1851. Lesions in animals from injection of foreign serum or of streptococci which more or less resemble Aschoff bodies do not prove much. None of my rheumatic fever patients has had serum and all of us have had repeated streptococcal infections. Perhaps we are all rheumatic. But why some more so? The same question could perhaps be asked about serum sickness which only occurs in 5% of exposées.

Dermatomyositis.—We know even less about this than these other diseases. Some cases have vascular lesions but these do not resemble polyarteritis nodosa. Some have a preceding history of repeated tonsillitis; others, up to 15%, are associated with neoplasm or reticulosis and may heal with successful treatment of the neoplasm. This recalls the Coombs-positive hæmolytic anæmia seen sometimes with reticuloses. If these dermatomyositis cases have incomplete antibody absorbed on to the muscle cells, this has not yet been demonstrated.

Scleroderma.—There is here little evidence that suggests hypersensitivity, although a number of patients have arterial lesions and fibrinoid which somewhat resemble the change in lupus.

In *acute lupus erythematosus* there is suggestive evidence of a disease involving hypersensitivity, possibly of the auto-immunization variety. The fibrinoid material is often widely distributed and probably originates in the hæmatoxylin bodies which come from nucleoprotein. Sometimes this transition can be seen histologically in the heart valve.

The nuclear breakdown is thought to be associated with the factor in serum which causes normal leucocyte nuclei to be broken down and ingested by polymorphonuclears. This serum factor is a γ-globulin and is postulated to penetrate the cell and to inactivate the desoxyribonuclease inhibitor normally present therein and therefore allow nuclear degradation to proceed. A comparable change in human leucocytes has been produced by antileucocyte serum.

The L.E. cell phenomenon has recently been reported in the sera of patients with hypersensitivity reactions due to penicillin, in patients given Hydrallazine for hypertension and accompanied by clinical symptoms resembling lupus erythematosus, and in acute virus hepatitis. The first of these conditions is by definition associated with hypersensitivity; the second may be a drug sensitivity since it responds on withdrawal of the drug and the third

is thought by Joske and King to be similar to the alteration of cells produced by virus infection or of antibody production by reticulo-endothelial tumours which brings about the serological changes of symptomatic hæmolytic anæmia. Many cases of acute lupus erythematosus show a positive Coombs test, and some are first manifest as acute hæmolytic anæmia or thrombocytopenic purpura. While the globulin absorbed on to the red cells in hæmolytic anæmia has not yet been proved to be antibody, in the sense that it has been produced in animals by injection of the appropriate antigen, there are many facts which suggest that this globulin is an antibody, similar to the incomplete antibody of Rhesus sensitization. Thus it is usually a γ-globulin, it may show specificity for certain blood group antigens, hæmolysis of trypsinized red cells may be produced in the presence of complement and Coombs-positive sera, the warm type is inhibited by γ-globulin and it may be accompanied by other antibodies. In lupus, also, there is an increased tendency to form iso-agglutinins after blood transfusion, and not infrequently false positive W.R.s and Kahns, i.e. substances reacting with Kahn antigen. However, if lupus is a disease of auto-immunization, we do not know what antigenic substance is involved nor how it is rendered auto-antigenic.

This disease is associated in a very complex way with *rheumatoid arthritis*. A number of patients with lupus erythematosus have presented a clinical picture for several years indistinguishable from rheumatoid arthritis. Occasionally in patients with rheumatoid arthritis of many years' duration and without any of the symptoms of lupus, L.E. cells may be found. In rheumatoid arthritis the evidence for hypersensitivity is far less impressive. The characteristic cell type of the tissue lesion, however, is the plasma cell which is known to be associated with the production of antibody protein, and the serum shows an increase in γ-globulin. The only characteristic serological factor is that part of the γ-globulin which produces agglutination of sensitized sheep cells—the Rose-Waaler test.

This test is positive in most cases of rheumatoid arthritis and lupus erythematosus, but we are quite ignorant of its meaning. Both these diseases, together with polyarteritis and dermatomyositis, differ from acute and self-limited collagen diseases in that the course is protracted often over many years and, if they are diseases of hypersensitivity, one must postulate that the antigenic or haptenic substance must be present in the body throughout this long period of activity.

In *polyarteritis nodosa* evidence for hypersensitivity depends upon the reported cases which have occurred following drug therapy, &c., and upon the production of a similar arteritis by serum and especially albumin injections in experimental animals. It must be remembered, however, that similar lesions have also been produced by hormones, high salt diet, &c., and that there may be several types with different ætiological mechanisms within the polyarteritis group. One of these types is associated in an intimate way with asthma, eosinophilia and sinusitis, and produces granulomata in the kidneys and other organs somewhat resembling the granulomatous nodules of rheumatoid arthritis and lupus erythematosus. If polyarteritis nodosa or any one type of it is a hypersensitivity lesion, it is important to define the suspected antigens and in particular to investigate closely those cases to whom no drugs have apparently been given.

Finally, along what lines should we look for further evidence for or against the hypersensitivity hypotheses? It is essential that proof provided should refer to man. The simplest *in vivo* test and one without any risk is removal of the patient from exposure to the suspected antigen and this we can accomplish in rheumatic fever with chemoprophylaxis. Others such as patch, scratch and intradermal testing are accompanied by a slight element of risk and are unlikely to be a great deal of help in most of the diseases I have mentioned. They are seldom useful in drug allergy without dermatitis. Passive transfer of circulating or cell-fixed antibody and its testing in a normal recipient by the suspected antigen again demands that the antigen should be known, and there is also here a slight risk of transmitting jaundice. *In vitro* testing is obviously the safest and in many ways the most reliable, but the classical methods for demonstrating antibody such as precipitation or complement fixation are of little value in these diseases. It is probable that further work on cell-fixed antibody of which we know very little at the moment would be the most favourable line of attack.

Dr. G. A. Rose:

Infections and Their Treatment in the Ætiology of Polyarteritis Nodosa

It is often stated categorically that polyarteritis nodosa is due to hypersensitivity to drugs. This view originated in the report by Clark and Kaplan (1937) of the finding of arteritis at necropsy in 2 cases which had been diagnosed clinically as serum sickness. Subsequently Rich (1942) described 6 more proven cases of polyarteritis which followed an illness with the features of serum sickness. Such an association was not described again; but there

followed a series of reports in which polyarteritis was observed to follow the sulphonamide treatment of respiratory infections. With negligible further evidence of sulphonamide hypersensitivity, the theory of drug sensitization continued to gain strength, largely through repetition. In recent years it has been extended to include such drugs as dichlorodiphenyltrichloroethane (D.D.T.: Hill and Damiani, 1946), dilantin sodium (Van Wyk and Hoffmann, 1948), penicillin (Waugh, 1952), and a combination of penicillin, streptomycin, isoniazid and cortisone (Edge *et al.*, 1955). Clearly it is desirable that the basic evidence for incriminating drugs should be reassessed; for if this is not conclusive, then all these isolated case reports of polyarteritis following the use of this or that drug add nothing to the weight of evidence.

Evidence of a causal relation between drug administration and the onset of polyarteritis may be of two types:

(1) *Evidence that a particular treatment preceded the onset of the disease more often than would be expected by chance.*—In the case of a commonly used drug, such evidence is significant only if the association is observed commonly. It introduces the possibility of several erroneous interpretations. For instance, in some cases (such as that of Edge *et al.*, 1955) it seems extremely probable that the onset of polyarteritis has been misdated, and that the disease was, in fact, already established before the suspected drug was given. Such a possibility must also be considered in the cases in which serum therapy was blamed; for the symptoms which were attributed to serum sickness might possibly all have been due to polyarteritis. Another danger in interpretation which has sometimes been overlooked is that the significant association (if any) may be the condition for which the drug was given, and not the drug itself. This consideration applies especially to respiratory infections, which have been the commonest reason for giving the suspected drugs.

(2) *Evidence that exacerbations of the disease repeatedly followed the giving of a particular drug.*—This type of evidence is potentially much more convincing, but it has been observed only rarely. In the case of sulphonamides the nearest approach to it seems to be the case recorded by Goodman (1948). Here polyarteritis appeared shortly after the sulphonamide treatment of a sore throat; a further course of the drug nine weeks later was followed by a severe reaction. Since, however, a complete and lasting remission began only one week later, it is hard to say whether sulphonamide sensitivity was more than coincidental.

In the case of thiouracil there is more convincing evidence. Dalgleish (1952) described a patient who developed polyarteritis during a first course of thiouracil, and who suffered a fatal exacerbation following a second course; and McCormick (1950) reported a case in which exacerbations were closely related to 4 separate courses of the drug. I have personally observed 2 cases of clinically typical polyarteritis which began during thiouracil therapy but in which the pathological appearances of the arteritis were atypical. This does just raise the possibility that thiouracil polyarteritis might be distinct from ordinary polyarteritis.

Miller and Nelson (1945) have reported a case of fatal polyarteritis in which the terminal illness began one and a half hours after an injection of Mapharside. The patient (a syphilitic) had had transient minor reactions following injections of neoarsphenamine bromide five months previously. Taken by itself this case sounds quite suggestive of a causal relation between arsenic and polyarteritis; but the absence of any other similar reports, despite the common use of arsenical therapy, prevents the drawing of any definite conclusions.

An opportunity recently presented of collecting information from a large series of cases of polyarteritis. This survey, which I was enabled to carry out on behalf of the Medical Research Council, covered 111 proven cases that had been under care at various British teaching hospitals in the period 1946 to 1953. The Collagen Diseases and Hypersensitivity Panel of the Medical Research Council, which arranged the investigation, has kindly given me permission to quote some of the results. Of the 111 cases, 7 were atypical and were thought to represent different disease processes; the following figures are therefore based on the remaining 104 cases.

Conditions preceding the onset of polyarteritis.—In 9 patients there was a past history of rheumatic fever; most of these had chronic rheumatic heart disease. In 3 more patients the onset of polyarteritis was accompanied by typical rheumatic fever; and 1 other patient with no relevant history showed a subendocardial Aschoff node at necropsy. This makes a total of 12·5% of patients with evidence of past or active rheumatic fever; although uncontrolled, this figure is suggestively high. Furthermore there have been at least 7 previously reported cases in which typical Aschoff nodes were seen at necropsy in cases of polyarteritis (Rothstein and Welt, 1933; Spiegel, 1936; Rose *et al.*, 1950; Pagel, 1951).

In 26 patients (25%) there was a history of bronchiectasis or chronic bronchitis preceding the onset of polyarteritis, usually by many years. There was no evidence that these infections were of an unusual type, either bacteriologically or pathologically. By contrast, of

the 22 patients who had specific polyarteritic lesions in the lungs and in whom the sputum had been cultured, one-quarter yielded a growth of hæmolytic streptococci. This is a most unusual organism to find in other types of chronic lung disease. This group of polyarteritic patients showed a number of features which distinguished them from cases without lung involvement. One of these characteristics was that the clinical illness associated with the lung lesions preceded the appearance of generalized polyarteritis, usually by months and sometimes by years. This made it difficult to obtain information on these patients about acute illnesses preceding the original onset of the disease. But in the remaining 66 patients without lung involvement the following figures were obtained: 12 patients (18%) had had sore throats or tonsillitis within six weeks of the onset of polyarteritis, the usual interval being two weeks; and in at least 8 of them the infection was attributable to hæmolytic streptococci. 5 other patients were recorded as having had a cough within six weeks of the start of polyarteritis. At least 3 of the patients with recent streptococcal infections had definitely received no drugs. On the other hand a total of 7 patients (11%) had recently been treated with sulphonamides.

Observations made during the course of the disease.—Sulphonamides were administered after the onset of polyarteritis to 24 patients. In one instance an initial course was followed by urticaria, but a second course was without complications. In the remaining patients the treatment appeared to be entirely without effect. With the exception of cortisone and corticotrophin the same was true of a wide variety of other drugs, including antihistamines and antibiotics of all sorts.

There was no evidence that the manifestations of histamine-type hypersensitivity occurred with undue frequency. An "urticarial" rash was recorded in 5 patients; but in 3 of them it seemed possible that the diagnosis was wrong, and that the rash was, in fact, that of cutaneous polyarteritis. Asthma was quite common. But with one exception it was restricted to the group with lung lesions; there was no family history of allergy; the distribution of the patients' ages at onset was characteristic of polyarteritis rather than of allergic asthma; and there was usually a very high eosinophilia, of an order rarely seen in allergic asthma. It therefore seems that asthma in cases of polyarteritis is distinct from ordinary allergic asthma; its significance is thus uncertain. The same is true of eosinophilia. Although this is a common feature of hypersensitive states, it occurs also in conditions in which hypersensitivity is not known to play any part. In most cases of polyarteritis it is either absent or fairly slight. High eosinophilia (i.e. 1,500/c.mm. or more) is confined to patients with lung involvement, amongst whom it is very common. Symmers (1954) has described finding larvæ, probably those of *Ascaris lumbricoides*, in the lungs of 2 cases of eosinophilic polyarteritis. I have never seen this myself, and in the Medical Research Council series stool examinations for ova were negative in several eosinophilic cases. But the observation does suggest that evidence of parasitic infestations should be looked for with some care in these cases.

Conclusions as to the ætiology of polyarteritis.—It is clear from the observations so far presented that conclusions as to the ætiology of polyarteritis can only be very tentative. In the first place it seems probable that a few cases have been due to thiouracil hypersensitivity; but such cases are very rare, and there is some slight evidence that they may be distinct from ordinary cases of polyarteritis. The only clue likely to be relevant to a large group of cases is the frequent association with acute and chronic respiratory infections and their treatments. The most suspect organism is the hæmolytic streptococcus, and the most suspect drugs are the sulphonamides. The difficulty is to dissociate these two possible factors. The following evidence casts suspicion on the infection itself rather than on the treatment:

(1) In the Medical Research Council series at least 3 of the patients with recent streptococcal infections had definitely received no drugs up to the time of onset of polyarteritis.

(2) There is a not infrequent association with rheumatic fever, a disease which is closely related to streptococcal infection but not apparently to drug sensitivity.

(3) In almost all the recorded cases of polyarteritis following sulphonamide treatment, the drug has been given for a respiratory infection. Whereas, if the disease were due to sulphonamide hypersensitivity, one would have expected cases to occur equally with infections in other sites.

(4) In known examples of drug reactions (such as serum sickness, or the arteritis produced in rabbits by repeated serum injections) the period of active disease is relatively short. But in the Medical Research Council series the disease was still active in all but one of the patients who survived three months or more; and the characteristic pattern was one of

repeated exacerbations and partial remissions, apparently unrelated to the administration of drugs, and continuing sometimes for years. It is thus unsatisfactory to attribute the disease in this group of patients to the administration of a drug which was generally given only at the onset. It is more reasonable to suppose that drug hypersensitivity, if it is a factor at all, operates in those patients who die or recover within a short period of the onset of the disease. Even in these patients, however, there is the same suggestively high incidence of preceding respiratory infection.

It seems, then, that the available evidence on the whole favours hypersensitivity to respiratory infections (especially those due to streptococci) as the most likely cause in many cases. There is little clinical evidence, however, of histamine-type hypersensitivity; and the lesions are necrotizing and not (as in urticaria) œdematous. Thus the type of immunological abnormality involved is quite unknown.

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Professor G. Payling Wright:

Experimental Allergic Lesions in Animals

I shall describe briefly three interesting and possibly important allergic lesions in animals which have been studied intensively by experimental pathologists in recent years.

My first instance of this type of injury is the diffuse arteritis of rabbits that follows with considerable regularity their immunization with foreign proteins. Vascular lesions of this kind were first recorded by Boughton (1917) in animals that had been used by Longcope in his experiments on the role of hypersensitivity in the pathogenesis of nephritis. We owe most of our knowledge of these allergic vascular lesions, however, to German pathologists, and their observations were admirably reviewed by Klinge (1933) in his monograph on rheumatism.

When rabbits are injected with a foreign protein, usually some serum protein, signs of injury may in time appear in the aorta and in the muscular arteries of certain organs. The affected vessels show acute lesions characterized by marked focal accumulations in their intima and media of neutrophils, lymphocytes and histiocytes. Their collagen fibrils, too, become swollen, deeply eosinophil, and eventually show typical "fibrinoid" staining. Ultimately, reparative processes follow, and the media and adventitia exhibit minor grades of scar formation.

Before any parallelism between the experimental and the natural diseases is accepted too readily, certain facts must be taken into consideration which should seriously discourage investigators from any facile generalization. For it becomes immediately evident from a survey of the experimental papers that a rather monotonous uniformity of procedure has been followed to produce these vascular lesions. In all the studies, rabbits were used as the experimental animal, and this species restriction should not be overlooked when reflecting on the possible extrapolation of the findings to human disease phenomena. The sensitizing antigen employed was almost always horse serum—occasionally other antigens such as swine or bovine serum proteins, either in crude mixtures or in separated fractions, were used instead. In all those experiments which yielded positive findings, the animals had been strongly immunized and a high degree of sensitization had been induced. Finally, in most of the rabbits, the arteritis was limited to the coronary arteries of the heart—it was much less common in other organs. These lesions, which are not dissimilar to those described

as following "serum sickness" in man (Rich, 1942, 1945), are of too circumscribed a kind yet to warrant any assumption of an allergic ætiology for the much more widely distributed vascular damage in polyarteritis nodosa. Before this hypothesis can claim warmer consideration, it would seem essential to amplify our present knowledge both by using other antigens and by testing the vulnerability of other animal species.

My second example of an experimental allergic lesion that may present a parallel with certain diseases of man is the acute encephalomyelitis that can be produced by injections of emulsions or extractives of brain and spinal cord (for reviews, *see* Wolf, 1954, and Cavanagh, 1956). Although it has been known since the early days of pasteurian vaccination against rabies with emulsions of the spinal cord of rabbits infected with "virus fixe", that a small proportion of patients develop an acute, so-called "paralytic accident" (Hurst, 1932), it is only within the last decade that a comparable condition has been capable of consistent reproduction in animals and has come under close study as a possible analogue with certain well-known demyelinating diseases of man.

When monkeys are injected on repeated occasions with an emulsion of brain or spinal cord taken from a healthy animal of the same or a different species, no effects may be observed for weeks or months, but, after this lapse of time, some of them develop neurological disturbances, of which limb and ocular pareses, visual disturbances, tremor and muscular inco-ordination are the chief signs. As long as crude brain extracts alone were employed, such reactions were only obtainable with monkeys, but when the nervous tissue was emulsified together with the adjuvant of dead tubercle bacilli in an oily matrix, which Freund had found to encourage greatly the development of delayed allergic reactions generally, comparable results could also be produced in dogs, rabbits, guinea-pigs and other species. Moreover, with the aid of this adjuvant, the lesions appeared sooner and in a higher proportion of the animals inoculated; Kabat and his colleagues (1947), for instance, found that with monkeys, even a single inoculation with this brain-adjuvant mixture sometimes sufficed to produce a fatal reaction.

In animals killed or dying when the clinical manifestations are still conspicuous, numerous small foci of an acute inflammatory nature can be seen throughout the central nervous system and more especially in its white matter (*see* Ferraro and Roizin, 1954, for details). Most of these local lesions seem to be centred upon small blood vessels, especially upon venules, and contain many immigrant leucocytes in addition to the local microglial cells themselves. In those animals that survive the acute stage, the lesion subsides into a focal aggregation of microglial cells surrounded by a zone of demyelination. Still later, as Ferraro and Roizin have pointed out, the lesion may come to be represented by an irregular area of gliosis.

There can be little doubt that these small inflammatory lesions are essentially allergic in character. They only appear after either multiple inoculations of brain emulsions or after the employment of brain extractives fortified with adjuvants that are well recognized to promote the accelerated development of the allergic state. Furthermore, the condition is associated with the appearance of a specific delayed-type reaction to the intradermal inoculation of brain emulsions.

The validity of such experiments in providing analogues for certain well-recognized demyelinating diseases of man is still undecided. It seems to me unlikely that all the members of this diversified group of diseases will be accounted for on the basis of an allergic ætiology. In multiple sclerosis in particular, with its usually chronic, remittent but progressive course, the parallelism with the acute manifestations of experimental allergic encephalomyelitis seems especially difficult to sustain. But apart from the typically different clinical and morphological features of the human and animal diseases, the difficulties that beset any theory of an allergic ætiology for multiple sclerosis are formidable. The conditions under which the experimental lesions are evoked in animals are highly artificial—the amount of brain substance in the inocula required for a successful result constitutes a very large fraction of the total weight of the central nervous system of the animal affected, and the injections need to be repeated at intervals over a long period. Even when the inocula are fortified with the highly artificial adjuvant of tubercle bacilli in oil, the quantity of nervous tissue required is still large. It is hard to conceive any circumstances under which a human being could become sensitized to the proteolipids of his own nervous system, even as a sequel to extensive laceration of his brain as a result of trauma or some vascular accident. Nor is the analogy between the human and animal diseases brought closer by the observation of Stauffer and Waksman (1954) that whereas in experimental allergic encephalomyelitis circulating antibodies to brain antigens can be detected, they have found no such distinctive antibodies in the sera of patients at various stages of multiple sclerosis. Finally, as Greenfield (1954) has pointed out, in multiple sclerosis it is the myelin that is primarily and principally affected and in young plaques the evidence of acute inflammatory reactions of a kind so characteristic of the allergic lesions is slight or absent.

My third and last example is taken from the many attempts to reproduce in animals the lesions that characterize acute glomerulonephritis in man. Ever since Schick (1912) suggested more than forty years ago that this and some other complications of scarlet fever might have an allergic basis—largely because of the correspondence in point of time between the appearance of signs of renal injury and the development of circulating antibodies—many efforts have been made to replicate the condition in animals by experimental immunological procedures. In design they fall for the most part into two main groups: first, those in which, following Masugi (1933), heterologous nephrotoxic sera were employed to initiate the damage; and second, after Longcope (1915), those in which the animals were subjected to vigorous and usually repeated assaults by some antigen, usually some foreign serum protein.

The cardinal feature of the experiments of Masugi and his successors was the employment of a specific cytotoxic serum—in this instance a nephrotoxic serum—which had been prepared by the injection of renal tissue into some foreign species of animal. By inoculating finely divided suspensions of rat's kidneys into rabbits, they were able to prepare an "antikidney serum" which on injection into rats brought about serious injuries to their renal glomeruli. That the destructive effect of such a nephrotoxic serum was not restricted to the rat-rabbit combination was soon made clear by the finding that comparable heterologous antisera could be prepared against the kidneys of rabbits, dogs and other common laboratory animals. Later work has amplified these findings by showing that after their injection into the susceptible animal, the immune bodies in such antisera become specifically attached to certain structures in the renal glomerulus. Pressman and his colleagues (1950) have shown very elegantly by the use of autoradiographs, and Hill and Cruickshank (1953) by employing fluorescein-coupled antibodies, that labelled nephrotoxic antisera become firmly and specifically attached to elements in the glomerular tuft.

Through the use of a different technique, Longcope and his followers have created glomerular lesions in animals which in the opinion of many, though not of all, who have since used the method, resemble those of human glomerulonephritis. In most of these experiments, rabbits were used and the foreign serum or separated serum proteins were injected periodically, often at brief intervals for months on end, until the recipient animal had become highly sensitized. In a large proportion of these animals, signs of renal damage eventually appeared, and Hamilton-Paterson and Henderson (1952) have recently described the successive injuries suffered first by the glomerulus and later by the tubules as the state of hypersensitivity advanced.

The conclusion seems inescapable that under appropriate circumstances the glomerulus can be gravely damaged by a local reaction that is essentially immunological in character. If Schick's suggestion has any basis, acute glomerulonephritis in man must apparently depend upon either, first, some specific retention of an antigen—presumably of streptococcal origin—in the endothelial cells of the capillaries in the tuft, and the subsequent reaction of this antigen with its antibody when the latter is released by the reticulo-endothelial system of the patient some ten days or so later; or second, upon an immunological kinship between some components of the bacteria and the kidney which would lead to a specific reaction between the newly formed streptococcal antibody and the normally present renal analogue of the bacterial antigen.

Instances are already known of heterophil antigens of the Forssman type that are common to certain bacteria and to human red corpuscles. The pneumococcus Type 14, as Goebel and his colleagues (1939) have shown, has an antigen that is closely related immunologically to an antigen that is present in human Group A red corpuscles—an observation that emerged from an analysis of the finding by Finland and Curnen (1938) that the intravenous administration of Type 14 antipneumococcal horse serum to patients is sometimes followed by severe hæmoglobinuria and occasionally by death. Some comparable kinship might similarly exist between an antigen in the hæmolytic streptococcus Type 12—the type that has been recovered with disproportionate frequency from the throats of patients suffering from acute nephritis—and some glomerular constituent of the human kidney. Were this so, the liberation of the specific antibody that follows infection with organisms of this type might lead to allergic reactions in the kidney similar in character to those brought about by a nephrotoxic serum. Distinctive antigenic components of fixed tissue cells are much more difficult to investigate than those of red corpuscles, but the progress that is now being made in the immunology of tissue grafting may well lead to the disclosure of more of these obscure heterophil relationships. However, any such hypothetical kinship between bacterial and tissue cell antigens is likely to prove to be closely specific for both, so that the lesions that develop in some natural disease in man may not be readily reproducible, or even reproducible at all, by exposure of common laboratory animals to the same bacterial antigen.

Our interpretation of allergic manifestations in man would obviously have been

impossible but for the early fundamental studies on anaphylaxis in dogs and guinea-pigs by Richet and Theobald Smith. But there is a danger that these past successes may make us over-confident and that we may presuppose too much from the many biochemical and pharmacological reactions that are common to man and the usual laboratory mammals. Whether the observations on the three allergic lesions in laboratory animals which I have just briefly reviewed, will, either collectively or individually, provide rewarding analogues for human diseases, time alone will disclose. But we must exercise great caution in any attempt to translate discoveries made in the experimental pathological laboratory for the interpretation of clinical syndromes met with in the wards. More especially must we be on our guard in making inferences respecting their ætiology.

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Dr. D. A. Long (National Institute for Medical Research, Mill Hill):

Experimental Pathology and Collagen Diseases

Klinge (1929, 1933) introduced the concept of a group of systemic diseases affecting connective tissue. Klemperer (1950, 1951) suggested the collective term "collagen diseases" to indicate the site of the characteristic lesion—fibrinoid necrosis. The term was never intended for use in the diagnostic sense, but merely to underline the histological analogy. The collagen diseases resemble each other in many ways (Table I). We argue, by analogy,

TABLE I.—THE ANALOGY BETWEEN THE SYMPTOMS OF THE DISEASES OF COLLAGEN

	Heart and vascular lesions	Lympha-denopathy	Hyper-γ globu-linæmia	Nodules	Fibrinoid necrosis	Serositis	Arthritis	Main damage
Rheumatic fever	+	(+)	+	+	+	+	+	Heart.
Rheumatoid arthritis	+	+	+	+	+	+	+	Joints.
Lupus erythematosus disseminatus	+	+	+	+	+	+	+	Diffuse.
Polyarteritis nodosa	+	+	+	+	+	+	+	Diffuse.
Dermatomyositis	(+)	+	+	+	+	(+)	+	Skin, muscle.
Scleroderma	+	O	(+)	O	+	O	+	Skin.

that they are therefore likely to resemble each other in other ways (*see* Jevons, 1931), for instance, in response to cortisone. By this means, knowledge of one member of the group (i.e. rheumatic fever) may result in new facts about the group as a whole.

The experimental pathologist selects features which are common to a group of diseases so that he can study, under controlled conditions, their relationships to each other. If he is logical in his approach he makes further use of argument by analogy to choose an animal that resembles man in those features selected for study (Long, 1954, 1955).

Factors common to the collagen diseases.—The collagen diseases are systemic, not local, diseases. Klinge thought that "fibrinoid necrosis" was presumptive evidence of a hypersensitivity reaction. Certainly systemic diseases of this type have not been shown to occur in the absence of naturally occurring or artificially induced allergic reactions. Klemperer (1951) pointed out that fibrinoid necrosis occurs locally in the base of gastric ulcers and can be produced locally by mechanical means. But Klemperer's observations do not disprove Klinge's allergic hypothesis, which was applied only to systemic disease.

In these "collagen diseases", all tissues derived from primitive mesenchyme—connective tissue, reticulum, muscle, cartilage and bone—are involved in varying degree. The actual syndrome depends on the degree of damage at any particular site (Table I). The basic pathological process differs little between syndromes, but lesions in heart, blood vessels, joints or serous membranes each provide characteristic symptoms. Indeed, features of more than one syndrome may occur concurrently in a single case; alternatively, a collagen disease may start with one syndrome predominating and as the disease progresses this syndrome is replaced by another. In each case, characteristic cellular infiltration and fibrinoid necrosis with extracellular deposition of abnormal protein (Klemperer, 1951) are associated with lymphoid hyperplasia and hypergammaglobulinæmia. The latter may represent a primitive defence mechanism (Aegerter and Long, 1949), or a direct or indirect response of the tissues to allergens or antigens (Long, 1954, 1955).

The pathology of the early stages of these diseases is less certain. The earliest lesion in an analogous disease in guinea-pigs is œdema (Long, 1954, 1955). Very recently, œdema has been shown to occur early in rheumatoid arthritis (Kulka *et al.*, 1955). In each case, the development of œdema is soon associated with infiltration by mononuclear cells.

Hypersensitivity reactions.—Serum sickness and drug sensitivity induce in man analogous lesions in heart, blood vessels, joint and serous membranes. Similar lesions can be produced in animals by various types of allergic response. These can be divided into immediate and delayed responses (Table II). They involve widely different mechanisms, the characteristic features of which are tabulated (Table III). Immediate reactions can be divided into systemic

TABLE II

			Antigen	*Antibody*
Allergic responses	Immediate	Systemic [anaphylaxis]	Foreign	Host [Arthus or anaphylaxis]
			Host	Foreign [iso-sensitization]
			Host	Host [auto-sensitization]
		Local [Arthus]		
	Delayed [bacterial allergy]			

TABLE III

Anaphylaxis*	Bacterial allergy (Tuberculin type)
Artificial phenomenon	Natural phenomenon
Single injection of allergen induces sensitivity	Persistent low-grade infection induces sensitivity
Response immediate	Response delayed
Circulating antibody	Fixed antibody
The sensitive state can be passively transferred with serum (not cells)	The sensitive state can be passively transferred with cells (not serum)
Histamine has a major role in inducing symptoms	Histamine has a minor role in inducing symptoms
Anti-histamines diminish symptoms	Anti-histamines do not diminish symptoms
Cortisone does not diminish symptoms†	Cortisone diminishes symptoms
The characteristic lesion is spasm of smooth muscle	The characteristic lesion is the inflammatory necrotizing response

*The Arthus phenomenon can be considered as a type of "local anaphylaxis" affecting smooth muscle of blood vessels.

†In cortisone-sensitive species it is possible to depress the level of circulating antibody and so diminish anaphylaxis. This table is based on work carried out in cortisone-resistant species—species analogous to man (Long, 1955). An appreciation of the basis of this subdivision is essential for an understanding of problems concerning the influence of hormones upon immune and allergic reactions.

or local; both result from union of allergen and circulating antibody. Variations of the technique can be introduced by varying the source of antigen and antibody between donor and recipient (Table II), though at the cost of weakening an already feeble analogy with naturally occurring disease in man.

In contrast, the delayed type of hypersensitivity reaction occurs in rheumatic fever (Long, 1954) and may occur in the other diseases of collagen. It is a natural, not a laboratory, phenomenon. It is a normal sequence of bacterial infection so that there is no need to postulate an abnormal hypersensitivity reaction (Report by the Scientific Advisory Committee of the Empire Rheumatism Council, 1950). For example, normal people become tuberculin positive after infection with tubercle bacilli and sensitive to streptococcal allergens after infection with streptococci. In the former case, a hypersensitivity reaction is produced by any strain of tubercle bacillus and in the latter case by any type of group A streptococcus. The group A streptococcus has another remarkable property which it shares with the tubercle bacillus. It may lie dormant in an immune host for long periods of time, but remain a potential source of danger (Denny and Thomas, 1955). It is important not to confuse this phenomenon with the old concept of focal sepsis (Long, 1955).

Endocrine factors.—The early stages of bacterial infection are associated with invasion and toxæmia. The resulting stress causes adrenocortical hyperactivity and catabolism of body protein. This process ends as immunity develops. Convalescence is associated not only with repair of local damage but with anabolism of body protein. To make this possible, adrenocortical activity decreases and insulin output increases. If bacteria persist, hyper-immunity to toxins and hypersensitivity to allergens are associated effects (Long, 1954, 1955). At this stage, the artificial reintroduction of increased adrenocortical activity, by means of corticotrophin or cortisone therapy, depresses sensitivity to bacterial allergens.

The experimental animal.—Man, monkey and guinea-pig are readily sensitized to bacterial allergens, are unable to synthesize ascorbic acid, and are resistant to the toxic actions of large doses of cortisone (Table IV) (Long, 1954, 1955). They are also resistant to

TABLE IV

Species	Tuberculin sensitivity	Ascorbic acid synthesis	Response to cortisone
Man, Monkey, Guinea-pig	Readily induced	Ascorbic acid not synthesized	Resistant (Antitoxin synthesis not depressed)
Rat, Mouse, Rabbit, Ferret	Not readily induced	Ascorbic acid synthesized	Sensitive (Antitoxin synthesis markedly depressed)*

*Antitoxin effect not known for ferret.

the diabetic action of alloxan. The guinea-pig and monkey tend to have a high level of non-protein –SH (Long, 1955). In all these respects they differ from the rat, mouse, rabbit and ferret.

An attempt has been made to assess factors common to the collagen diseases and the possible role of the experimental pathologist in elucidating their relationship to each other. The logic of the problem has been briefly discussed and clues selected that appear important to the author. Experiments to relate the many factors mentioned have been reviewed elsewhere (Long, 1955, 1956).

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BOOK REVIEWS

General Endocrinology. By C. Donnell Turner, Ph.D. 2nd edition. (Pp. xi+553; illustrated. 56s.) Philadelphia and London: W. B. Saunders Co. 1955.

In the production of this book, which is incidentally a new and revised edition, the author has had the avowed intention of breaking away from the idea, apparently current in some quarters, that endocrinology is a branch of clinical medicine. All will agree that the subject really embraces considerably wider fields and Starling's definition of a hormone has had to be extended to narrow the distance at which some of these substances operate. Until more is known of the nature of hormones in tissues, as distinct from those of accepted enzymes, the definition of a hormone to some extent remains arbitrary. The subject matter is the kind expected from a biological author, and the book is evidently intended primarily as a text for students in biology. It should also have an appeal to physiologists. It is perhaps rather too big to expect medical students to read it fully and is a little lacking in some of the important biochemical aspects. The general plan is a conventional one, the ductless glands being described *seriatim*. In addition there are most interesting chapters dealing with invertebrates and miscellaneous matters such as neurosecretion, plant hormones and embryonic organisms. It is these matters and the emphasis on pre-human vertebrate endocrinology which are noteworthy. There are short references in most of the chapters to clinical aspects so that the perspective as a whole is commendable. The fact that development of some branches of the subject such as parathyroid physiology originated in man is acknowledged. It is rather a pity that with so few illustrations the author selected such an atypical example of Simmonds' disease, which will help to perpetuate the mistaken notion that cachexia is an important feature of this condition. A picture of the common type of adrenogenital virilism rather than that of a boy with an adrenocortical tumour would also perhaps strike a better balance. We are told that "the use of iodine after thyroidectomy is a general routine procedure" and from the reviewer's interpretation that progesterone is quantitatively excreted in the urine as pregnandiol. The general information gained from the use of radioactive iodine is rather scantily treated. Probably the important subject of hormone assay, even by biological methods, is deliberately avoided. On the other hand a whole chapter is devoted to the views of Selye and here the author has not taken the opportunity to introduce some simplification of the original ideas and terminology for the benefit of the student. Indeed from time to time the reader would welcome some improvement in the lucidity of the prose. With such criticisms aside, the book is a valuable attempt to bring together information which tends to be unduly scattered and contains a sufficient bibliography to be valuable as a starting point of enquiry for the more serious reader.

The Pregnancy Toxæmias or the Encymonic Atelositeses. By G. W. Theobald, M.A., M.D., F.R.C.S.Ed., F.I.C.S., F.R.C.O.G., M.R.C.P. (Pp. xiv+488; illustrated. 63s.) London: Henry Kimpton. 1955.

The book itself is beautifully produced and is very clearly printed on good quality paper. But when he started reading it, the reviewer's mystification began at the title page when the sub-title ENCYMONIC ATELOSITESES was utterly beyond his comprehension. His mystification increased as slow but steady progress was made in reading through the first two Parts of the book which take about two-thirds of the total page space. In these Parts the author seems to have collected everything which was ever thought or said or written about pre-eclamptic toxæmia and allied subjects including of course, water metabolism, the pregnancy-lactation syndrome, etc., etc. The majority of the expressed views are given references—in one page alone there are 15 authors mentioned with their references and other pages may well have exhibited even more names. After much intense reading the ordinary person is left aghast at the enormous amount of knowledge and speculation which has been laid before him and is utterly unable to comprehend what it is all about.

One might talk about being unable to see the wood for the trees and even carry the analogy further. Just as one approaches the end of a dark wood and begins to perceive glimmerings of light so, here also, as one reads Parts III and IV, enlightenment starts and much information can be gleaned. Indeed, prior to these two Parts there were some very lucid and helpful portions, e.g. the Sections on the adrenal cortex, on fibrinogenopænia, etc. But the practical obstetrician will derive most help from reading the last one-third of the book. The earlier two-thirds can serve as a well-referenced symposium of the innumerable theories and pieces of research concerning the toxæmias of pregnancy.

Ophthalmology. A textbook for diploma students. By Patrick D. Trevor-Roper, M.A., M.B., B.Chir.(Cantab.), F.R.C.S., D.O.M.S.(Eng.). (Pp. xii+656; illustrated. 75s.) London: Lloyd-Luke (Medical Books) Ltd. 1955.

Traditional Moorfields teaching still forms the background of British ophthalmological instruction and a textbook of moderate size designedly based upon it will be welcomed by students, and especially by those from overseas, who are preparing for the Diploma examination. It is to those that this book is primarily addressed and it covers in its 656 pages the anatomy, physiology and optics of the eye (which occupy almost half of the volume); diseases of the ocular adnexæ and outer eye; and those of the inner eye and visual pathways.

The anatomical and physiological ground is well covered in the early chapters; although one feels that in some places a more succinct expression of such unifying concepts as the role of the binocular movements would be welcome. The presentation of the Section on optics is admirably practical.

In the chapters dealing with ocular disease, affections of the eye itself are dealt with lucidly with the aid of numerous illustrations. The inclusion of operative details—essential in such a work as this—of necessity limits discussion and description of clinical detail to a certain extent; and advice on treatment and prognosis are perforce at times a brief expression of aggregate opinion. In the chapters dealing with orbital diseases and with those affecting the visual pathways, where the authorities are less exclusively ophthalmological, this treatment of the subject is somewhat less successful.

The book can be recommended for its purpose: it is well produced and adequately illustrated. More colour plates, especially of the colour photographs now so beautifully made at the Institute of Ophthalmology, would be welcome; but here the limitations of expense are obviously decisive.

Studies in the Functions and Design of Hospitals. Nuffield Provincial Hospitals Trust. (Pp. xx+192; 131 figures. 63s.) London: Geoffrey Cumberlege, Oxford University Press. 1955.

This book is the result of an investigation started in 1949 sponsored by the Nuffield Provincial Hospitals Trust and the University of Bristol. A team of twelve, each a specialist in different subjects, under the chairmanship of an architect worked for five years on research into the design of hospitals.

There can be few buildings more complex than hospitals. Before the war several firms of architects specialized in this work and periodically competitions were held which discovered fresh designers. The building of hospitals has been interrupted for nearly fifteen years so that many of the people who had experience of this work are no longer available. During this time medical science has advanced and the National Health Service has been introduced so that the control of building will be different in the future from what it has been in the past. The Ministry of Health has embarked on an extensive scheme of new construction which will include new hospitals, extensions to existing hospitals and entirely new types of buildings, such as health centres, occasioned by the new organization of medical services.

The report of this investigating team has therefore come at a most opportune time. It is a model of its kind and one would like to see similar work carried out for other types of buildings. All too often an architect's brief is based on the past practice of his clients with little fundamental thinking about future needs and changed organization.

This investigation was made by studying in detail each process carried out in a hospital. The history of hospital design and a comparison of the best modern practices revealed a steady progress of development. It is astonishing how often Florence Nightingale hit the nail on the head, and many of her conclusions are as apt today as they were in her time. The patient is much the same as he always was; it is the methods of treating his troubles which have changed so much.

The work of the investigators has been put to full-scale tests and the team designed the following buildings which now illustrate the results of their experiments in everyday use—a sixty-four bed medical ward at Larkfield Hospital, Greenock; an eight-bed surgical unit and an operating suite for Musgrave Park Hospital, Belfast; and the Nuffield Diagnostic Centre at Corby.

One general conclusion seems to apply to the reports on all the processes studied namely that with better planning and organization much time and effort can be saved by nearly everybody working in a hospital. One is also left with a strong impression that many of the improvements suggested could be put into operation in existing establishments without much structural alteration. It is for this reason, quite apart from the fascination of the book itself, that one can commend it to medical men whether they are concerned with new building or with making the best use of what they have got.

Section of Neurology

President—REDVERS IRONSIDE, F.R.C.P.

[*November* 3, 1955]

CLINICAL MEETING AT THE NATIONAL HOSPITAL FOR NERVOUS DISEASES, QUEEN SQUARE, LONDON

Quadriplegia due to Exostosis of Axis.—K. W. E. PAINE, F.R.C.S.

The patient was a 20-year-old girl admitted to the National Hospital under the care of Dr. M. J. McArdle on August 30, 1955, and later transferred to the care of Mr. Wylie McKissock.

The main complaints were of difficulty in using the right hand and giving way of the right leg in the past seventeen months.

In November 1953 she had fallen off her bicycle and suffered some injury to her right hand and ankle. She remembered falling but was not able to give any satisfactory account of why she had fallen. She was unable to describe the injury to her right arm and leg except that there was weakness and swelling. She regained full use of these limbs in a week or two.

In March 1955 she again fell off her bicycle. Again she had weakness and swelling of the right hand and ankle. Two weeks later the right leg had let her down when she was walking and this had happened a number of times since then. The weakness of the leg had been progressive but she had been able to walk up to the time of admission.

At approximately the same time as she had noticed the weakness of the leg she was aware of the weakness of the right hand. This had also progressed and in addition the ring and little fingers had become flexed into the palm. The hand at the time of admission was of very little use to the patient.

Two to three weeks after the onset of the weakness of the hand and leg the patient had noticed loss of feeling of the right arm below the elbow and the right leg below the knee. This loss of feeling was associated with a sensation of "pins and needles" in the right foot but never in the hand.

In the six weeks before admission she had had attacks three to four times a day, in which involuntary extension of the elbow and abduction of the shoulder occurred. The right arm remained in the abnormal position for about five minutes before returning to its previous state. There had never been any involuntary movements of the leg.

On examination the patient was a pleasant, co-operative girl of average intelligence. There was no dysphasia or dysarthria. She had a dorsal scoliosis convex to the right. Cervical spinal movements were full and forced movements in any direction failed to produce any parasthesiæ or pain.

The right pupil was smaller than the left and there was a slight ptosis on the right.

The ring and little fingers of the right hand were flexed into the palm and could not be extended voluntarily. There was slight wasting of all muscle groups of the right arm most marked in the intrinsic muscles of the hand. No involuntary movements were seen. There was severe weakness of abduction of the shoulder, extension of the elbow, wrist and fingers and abduction and adduction of the fingers of the right arm, and moderate weakness of adduction of the shoulder, and flexion of the elbow, wrist and fingers of this arm. Co-ordination was impaired within the limits of the weakness of the arm. Tendon reflexes were increased on both sides more on the right than the left.

She had a bilateral pes cavus with hammer toes. There was severe weakness of hip and knee flexion and dorsiflexion of the right foot and moderate weakness of hip extension, knee extension and plantar flexion. Both legs were slightly spastic with increased tendon reflexes, more on the right than the left, and bilateral extensor plantar responses.

The patient was only a fair witness for sensory testing but there was no doubt that she had impairment of sensation to light touch and pin-prick of the right side which was complete in the arm and less complete on the trunk and leg. The upper level of this impairment was in the upper neck. On the left side occasional light touches and pin-pricks were missed up to the same level and the sensation was said to be less acute than in the face.

Position sense was impaired in all joints of the right arm but not in the leg. Two-point discrimination was impaired in the right hand and to a lesser extent in the right foot. Stereognosis was very poor in the right hand. The abdominal reflexes were absent.

X-rays of the cervical spine (Fig. 1) show a mid-line bony projection arising from the arch of the axis and growing upwards and forwards. Myelogram showed a partial block but it was impossible to hold the Myodil in the region of the defect at C.1-2 level.

Operation (September 7, 1955) (Figs. 2, 3).—The arch of the atlas and exostosis were removed.

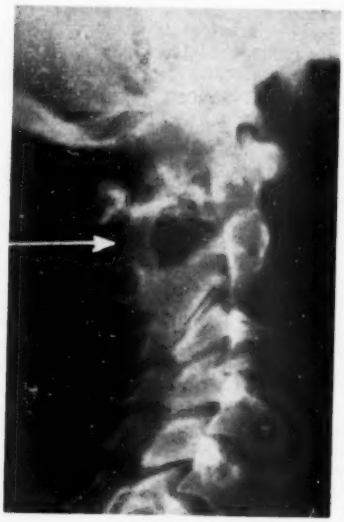


FIG. 1.

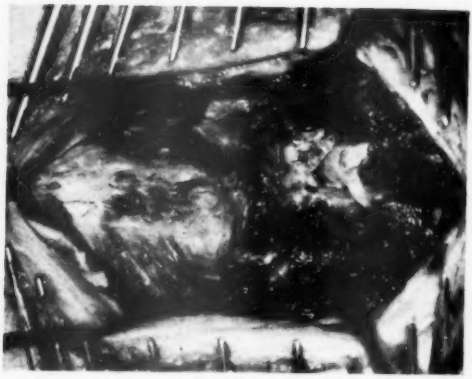


FIG. 2.

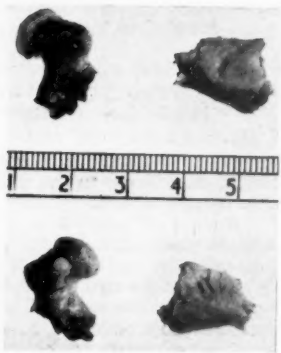


FIG. 3.

FIG. 1.—Lateral X-ray of upper cervical spine to show bony projection arising from the region of the spinous process of the axis.

FIG. 2.—Operation. View to show abnormal bony mass projecting anterior to the arch of the atlas and lying in a joint cavity.

FIG. 3.—Specimens removed at operation, on the left exostosis, on the right the arch of the atlas.

Discharge examination (19.9.55).—The Horner's syndrome was still present. The patient was able to extend her ring and little fingers of the right hand voluntarily and there was an increase in power of the other muscles of the arm. The sensory changes in the right arm were less marked and the lesser sensory changes on the left side could not now be demonstrated. The power of the right leg had also improved and she was fully ambulant. Both plantar responses were still extensor.

The case is of interest owing to the rare nature of the lesion causing paraplegia. At operation the appearance of the exostosis reminded me of those found in the condition of metaphyseal aclasia but this patient's long bones were X-rayed after operation without revealing any exostoses.

Two Cases of Intra-diploic, Intracranial Tumours.—G. F. SWANN, M.B., M.R.C.P., D.M.R. (for HUGH DAVIES, D.M.)

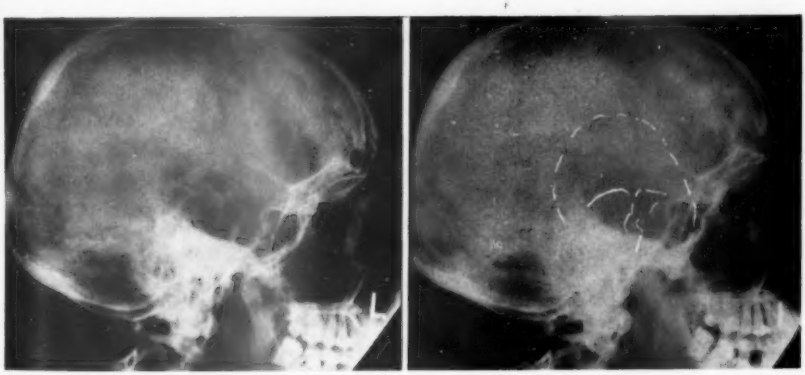
These are two cases of great radiological interest which presented with minimal signs but with dramatic, unexpected and somewhat similar radiological appearances.

Case I.—M. W., male, aged 22. Aircraftsman. Admitted to the National Hospital under the care of Dr. Denis Williams, complaining of involuntary movements of the right hand for five months. The present trouble started two years previously when he developed severe frontal headache. These headaches were associated with nausea and vomiting, they lasted about twenty-four hours, and three episodes, each lasting several days, occurred in the past two years. Five months previously he noticed unsteadiness and tremor of his right hand which gradually became worse, to such an extent that he had to shave and write with his left hand. It became worse with concentrated effort and, although always present, was least troublesome when the hand and arm were supported at rest. The other limbs were not affected. He also complained of some paræsthesiæ on the left side of the face, some dysphagia for liquids, and noticed difficulty in pronouncing the letter "L".

On examination.—No intellectual impairment was found. There was some bilateral proptosis (said to have been always present), and there was asymmetry of the skull with bulging on the left side in the temporo-parietal region. In his central nervous system there was bilateral papilloedema, a right upper quadrantic homonymous field defect, some minor loss of hearing in the left ear, and questionable diminution of pin-prick and temperature sensation of the first division of fifth cranial nerve on the left. The tremor was coarse, originating primarily in the proximal muscle groups; it disappeared almost completely if the arm was at rest, and was exaggerated by effort.

Investigations.—(1) EEG suggested a tumour seated deep in the left temporal lobe.

(2) Plain X-ray of skull showed areas of linear calcification on the left side, posterior to the sella, which had a rather soap-bubble appearance. In addition, there was a faint curvilinear area of calcification which, although not well seen in the reproductions, was well seen in the actual films. The sella showed pressure changes, the coronal suture was widened. A lateral view is shown with the areas of calcification marked in, and a full axial view shows widening of the left middle fossa, destruction of the tip of the petrous temporal bone, and an ill-defined anterior border to the margin of the left middle fossa (Fig. 1A, B, C).



A B

FIG. 1 (*Case I*).—A, shows the curvilinear calcification and soap-bubble appearance, together with widening of the coronal suture. B, shows the extent of the calcification marked in. C, full axial view showing destruction of the petrous temporal bone and floor of adjacent middle fossa.

(3) Left carotid arteriography showed, in lateral view, gross upward bowing of the sylvian group corresponding in its extent almost exactly with the crescentic calcification noted in the plain films. The A.P. view confirmed the lateral view appearances, and showed dislocation of the entire vascular tree on the left to the right. An oblique view showed both external and internal carotid filling (Fig. 2A, B, C).

As a result of the radiological investigations the following diagnoses were considered—cholesteatoma, calcified subdural hæmatoma and osteoclastoma. The diagnosis of an osteoclastoma, although sounding a little far-fetched, was suggested by Dr. R. Hoare who recalled a case published by Dinning (1953) which showed somewhat similar plain

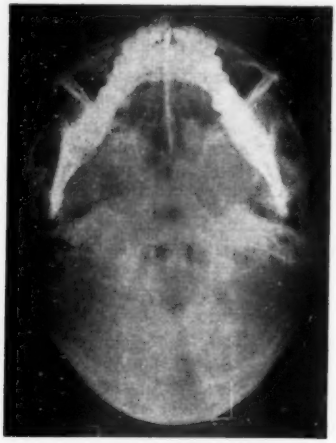


FIG. 1C.

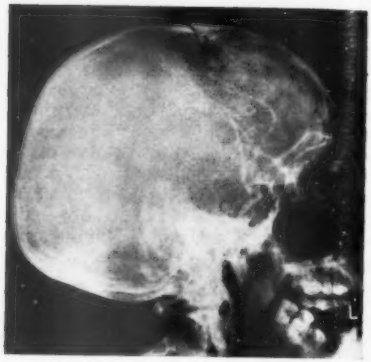


FIG. 2A.

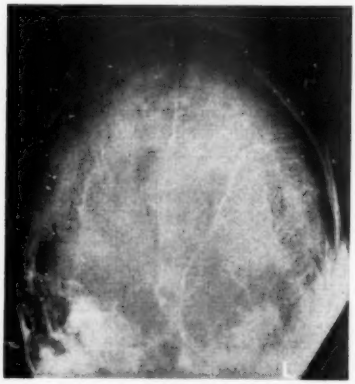


FIG. 2B.

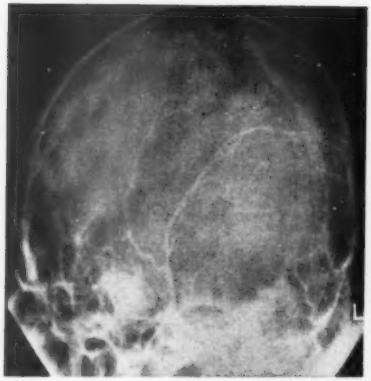


FIG. 2C.

FIG. 2 (*Case I*).—A, Upward sweeping of the sylvian group corresponding to the curvilinear calcification seen in the lateral straight X-ray view. B, Dislocation of the entire vascular tree on the left to the right, with stretching of the carotid near its bifurcation, gross medial displacement of the sylvian group and displacement of the anterior cerebral to the right. C, Oblique view showing external and internal carotid circulations. No pathological vessels were demonstrated.

X-ray changes to this case. Indeed, the changes in the squamous temporal bone, seen in the lateral view, do have the soap-bubble appearance often seen in osteoclastoma elsewhere. However, it was thought that the arteriogram ruled this out as both external and internal carotid circulations showed an absence of pathological vessels or venous lakes filled with contrast, which is said to be characteristic of the arteriographic manifestations of these tumours (de Santos—quoted by Sutton, 1955).

A calcified subdural hæmatoma is extremely rare in adults (Bull, 1940). Two cases were reported by Critchley and Meadows (1932), and Martin (1931), but in each of these cases the patient was a young adult with a history going back into earliest childhood and in which the malleability of the infantile skull had resulted in their survival.

The most favoured diagnosis was that of a cholesteatoma or epidermoid tumour, although it is uncommon for these to calcify intracranially (Shanks and Kerley, 1951). The bone defects in the skull vault, in addition, had not the clear cut, crescentic, sclerotic margin so often seen in this lesion (Schwartz and Collins, 1952).

The case was subsequently transferred to Mr. Wylie McKissock and I quote from his operation notes:

"The bone in the whole of the temporal region was thin and in the centre of the squamous part there was a defect. Removal of this part of the bone showed a tense, blue, cystic, extradural tumour which was multi-coloured, part vascular, part avascular, and contained multiple cysts. It extended medially and probably almost to the mid-line, and examination of the floor of the middle fossa again showed eroded bony defects. While removing the capsule thin plates of bone were found in several places suggesting that the tumour had arisen in the diploic space in the base of the lateral wall of the skull."

The tumour was completely removed.

Histological report recorded that it presented the features of a neurofibroma.

Mr. McKissock has not seen a similar tumour in twenty years' neurosurgical practice.

The patient made an uneventful and complete recovery.

Case II.—J. B., male, aged 18. Trainee draughtsman.

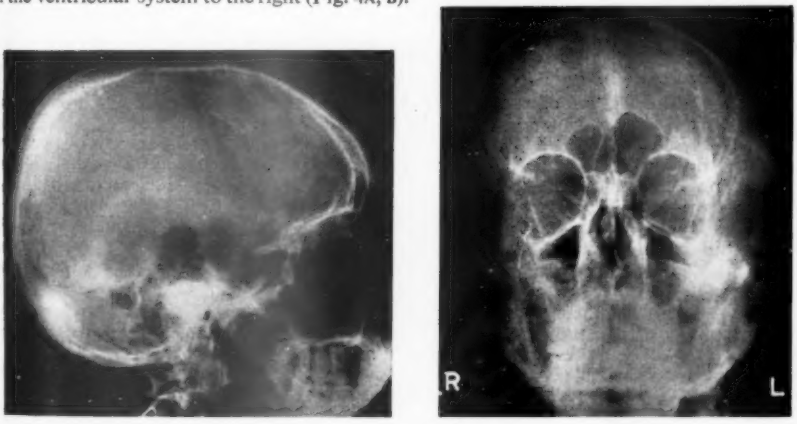
Admitted to the National Hospital under the care of Dr. S. P. Meadows, complaining of headache, nausea and blurring of vision. The headache had been present for three weeks, the blurring of vision for six days prior to admission. This was associated with inconstant diplopia.

On examination.—Bilateral papillœdema.

Investigations.—(1) EEG suggested a deep hemisphere lesion, which was left-sided and maximal in the temporal region.

(2) Plain X-ray of skull showed a large, round, calcified, intracranial mass in the left temporal region. The calcification in the mass was mainly peripheral and, in addition, there were three sharply defined areas of bone destruction with sclerotic margins. The pituitary fossa showed signs of raised intracranial pressure (Fig. 3A, B).

(3) Ventriculography confirmed the site of the tumour and showed quite marked shift of the ventricular system to the right (Fig. 4A, B).



A B

FIG. 3 (*Case II*).—A, round, apparently calcified tumour, with bone defects in the squamous temporal region which have a sharp, sclerotic, curvilinear margin. B, tumour in the left temporal region with bulging of the skull vault at this point.

A B

FIG. 4 (*Case II*).—Dislocation of the ventricular system to the right with squeezing of the left lateral ventricle in (A) antero-posterior and (B) lateral view.

At operation (Mr. Wylie McKissock) a large, cystic tumour was discovered which contained large quantities of candle-grease-like material characteristic of that found in cholesteatoma. The tumour was completely removed.

Histologically it was characteristic of a cholesteatoma.

The patient made an uneventful and complete recovery.

Summary.—These two cases have been presented as intra-diploic, intracranial tumours which were apparently calcified. They had arisen in the diploe of the skull vault and pushed before them a thinned layer of the inner table. It is important, from a radiological point of view, that this possibility should be appreciated and that the calcification of the tumours was apparent and not real, especially as calcification in epidermoid tumours is uncommon and almost unknown in neurofibromata.

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Brain-stem Angioma.—C. J. EARL, M.D., M.R.C.P. (for DENIS BRINTON, D.M., F.R.C.P.).

D. O., female, aged 27.

Aged 17: Sudden onset of nausea and drowsiness followed by weakness of left arm. Lumbar puncture showed blood-stained C.S.F. Full recovery.

Aged 19: Woke in the night—vomited and lost her senses. Found later to be ataxic and dysarthric with weakness of both internal recti and of right VI and nystagmus. Reflexes increased on right; bilateral extensors. Lumbar puncture again showed blood-stained fluid. Incomplete recovery.

Aged 27: Pain over right eyebrow. Paræsthesiæ in left arm and leg. Soon afterwards lost consciousness. C.S.F. blood-stained. Slow improvement since then. Signs on admission: Cerebellar dysarthria. Complete VI nerve palsy; nystagmus; right pupil smaller than left; motor V rt.; rt. facial weakness; mild right palatal weakness.

Limbs: Bilateral cerebellar ataxia—worse left than right and, in addition, moderate weakness of the left arm and leg with hyperactive reflexes and extensor plantar on that side. All forms of sensation are diminished over the left side.

Since admission she has developed a palatal nystagmus which is present now. Her ataxia and weakness have improved a little.

Vertebral arteriograms showed a large angiomatous malformation on the right side of the brain stem.

Mutism: for Diagnosis.—C. J. EARL, M.D., M.R.C.P. (for E. A. CARMICHAEL, C.B.E., F.R.C.P.).

C. D., boy, aged 10.

Complaints.—Inability to talk and difficulty in swallowing.

History.—Labour prolonged with forceps delivery. Said to have sucked normally but failed to stand till age 2, or to walk till 3, when mother noticed something wrong with his right arm and leg.

Aged 3: Onset of fits, which started in right arm and leg.

Aged 8: Speech indistinct.

On examination.—Jaw hangs open; face rather expressionless and saliva dribbles constantly from the corners of his mouth. He understands what is said to him and can indicate what he wants but cannot speak clearly. He has difficulty in swallowing and cannot keep his tongue protruded. There is a marked increase in the tone of the facial musculature on both sides with brisk contraction on tapping of the facial muscles. Limbs: Right side slightly small with slight weakness and increased reflexes.

Investigations.—A.E.G. showed slight enlargement of the ventricle on the left side. EEG: Left side very much more abnormal than right, with focus in left temporo-parietal region.

The differential diagnosis lies between lesions of the basal ganglia which have been described as causing this picture and bilateral cortical lesions in the lower part of the motor cortex, producing what is, in effect, a pseudo-bulbar palsy. In view of the mild right hemiparesis and slight enlargement of the left lateral ventricle, this was thought to be the more likely. The lesion presumably was more severe on the left side.

Unusual Case of Symptomatic Migraine.—GRAHAME WILSON, M.D. (for DENIS WILLIAMS, M.D., F.R.C.P.).

W. J., female, aged 19.

Her father and grandfather had suffered from migraine. The patient had a normal birth and her childhood development was normal. Since aged 3 years she had suffered from atypical migrainous headaches recurring at intervals of approximately six weeks, although at times the intervals were longer, and once two years elapsed between attacks.

These were heralded by nausea and vomiting which occurred after she had retired to bed for the night. This did not interfere with sleep but on awakening next day she always had a dull frontal headache, more pronounced over the left side. During the next twelve hours the headache gradually radiated over her head to the occiput, then disappeared. During this time she was nauseated and photophobic and preferred to lie in a darkened room. The attacks were often brought on by excitement or exposure to bright sunlight.

On 30.8.55 she went to bed as usual, awoke after half an hour feeling sick and vomited several times during the night. Next day she complained of dull frontal headache, nausea and mild giddiness. Several hours later the headache became much more severe and she again vomited. She then retired to bed but can remember little of the next two to three days, during which time she was confused and consistently complained of aching pain in her neck and left arm and leg. She was noted to have a weakness of the left external rectus muscle and examination of the cerebrospinal fluid showed xanthochromic staining.

When she regained full consciousness she had no complaints other than diplopia, the result of the left external rectus weakness, which slowly improved. She had no further attacks of headache.

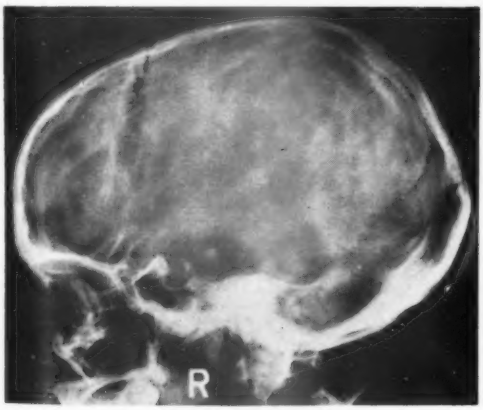


FIG. 1.—Plain X-rays of skull.

On examination. — Normal-looking girl of average intelligence; right-handed, and with no speech defect. The limbs were of normal development. There was slight left external rectus palsy and an equivocal right extensor plantar response.

X-ray of skull.—In the left parieto-occipital region and extending deeply towards the midline lay irregular flecks of calcification scattered over a wide area. The skull vault was asymmetrical, the left side being flattened in the lateral but slightly deeper in the vertical diameter. The skull sutures showed mild diastasis but the dorsum sellæ appeared to be normal (Fig. 1).

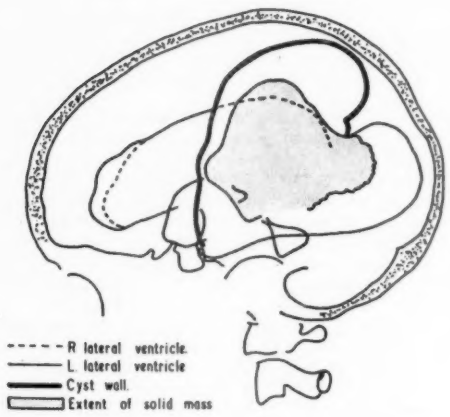
Electroencephalogram.—The alpha rhythm of 10 c/sec. was disturbed by frequent runs of high voltage delta waves in both occipital areas. Elsewhere the records were disturbed by slow and fast activity, with the addition of a focal abnormality in the left temporal region, consisting of irregular low voltage 2½–3 c/sec. waves.

Left carotid angiogram.—The left sylvian group of vessels were stretched and splayed out over the whole of their course, suggesting the presence of a hydrocephalus.

Ventriculogram.—Symmetrical dilatation of the anterior ends of both lateral ventricles, and although the septum pellucidum lay vertically it was situated 0·5 cm. to the right of

the mid-line due to the asymmetry of the skull. The third ventricle lay centrally but was dilated; the fourth ventricle was normal in size and position. In the left posterior parietal region lay a large porencephalic cyst in free communication with the lateral ventricle. Lying within the latter was a shadow cast by a large neoplasm which extended beyond the mid-line and roughly overlay the area of irregular calcification seen in the plain X-rays of the skull (Figs. 2 and 3).

Blood Wassermann negative.



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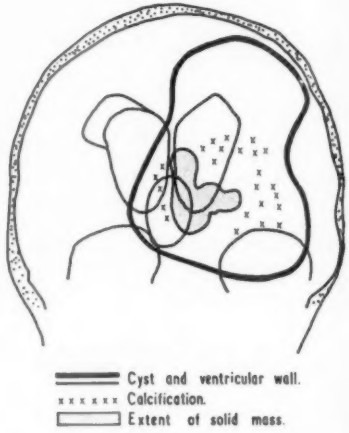

FIG. 3.

FIGS. 2 and 3.—Composite tracing of postero-anterior and lateral views of ventriculogram films.

Dr. Denis Williams thought the patient's attacks were due to an intermittent hydrocephalus produced by the benign tumour lying in the lateral ventricle. It was obvious that it had been present for many years and on first thoughts he questioned the advisability of surgical exploration as there was a definite risk of producing a permanent hemiplegia and aphasia. However, in view of her age and the probability of further attacks with deterioration in her condition he felt she would have to be explored.

Mr. K. W. E. Paine suggested that the tumour was a choroid-plexus papilloma.

Subsequent exploration by Mr. Wylie McKissock through a left parietal osteoplastic flap revealed a huge choroid-plexus papilloma which occupied most of the left lateral ventricle. During removal troublesome hæmorrhage was encountered from vessels at its base. Thereafter the patient was right hemiplegic and aphasic and died seven days later.

[*This Meeting will be continued*]